AN INTRAMOLECULAR DIELS-ALDER MODEL STUDY DIRECTED TOWARD THE SYNTHESIS OF (-)-MORPHINE

By

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A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL
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To my parents.
Thanks for all the love and constant support you have always given to me.

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AN INTRAMOLECULAR DIELS-ALDER MODEL STUDY DIRECTED TOWARD THE SYNTHESIS OF (-)-MORPHINE

By

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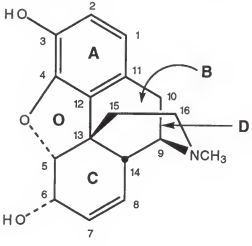
Chairman: Dr. Tomas Hudlicky
Major Department: Chemistry

An advanced model study describing a chemoenzymatic approach to a morphine fragment containing the 5 chiral centers found in natural (-)-morphine is described. The synthesis started with an enzymatic dihydroxylation of either (2-bromoethyl) or (2-azidoethyl)benzene to afford the corresponding chiral *cis*-dienediol. Proof of the stereochemical outcome of the key chemical step, an intramolecular Diels-Alder cycloaddition, was provided by X-ray crystallographic analysis. A previously reported analogous Diels-Alder cycloadduct was reinvestigated and a structure correction provided. Additional ether and ester tethered dienes were constructed to afford more advanced triene systems whose intramolecular Diels-Alder cycloadditions were investigated. Speculation on the results of the advanced studies was provided.

CHAPTER 1
INTRODUCTION

Of all the known active natural alkaloids, none has a history which rivals that of the principal opium alkaloid (-)-morphine **1**. Constituting some 10 to 20% by weight of more



1

than 50 alkaloids extracted from the sap of the unripened seed of the opium poppy[1] *Papaver somniferum*, morphine, named after the Greek god of dreams, has long been known for its analgesic and euphoric properties. Opium's first documented medicinal use was reported circa 1500 BC in the Smith and Ebers Papyri,[2] and its impact on society since these early times has been extremely significant. Today, morphine and its active synthetic derivatives have an established and consistent share of the pharmaceutical market.

Morphine has long been a challenging target for synthetic chemists. In spite of the previously reported 17 total or formal syntheses of morphine, a truly practical synthesis, which would rival the economy of isolation from natural opium, continues to elude the synthetic community. Both the ambiguity regarding the political and economic stability of the major opium producing nations (i.e., India, Thailand, Burma) and the continued

demand for the opium alkaloids suggest that the synthetic production of morphine and its derivatives might be necessary in the future. Thus, until an efficient synthesis of morphine has been accomplished, it will continue to be an attractive and challenging target.

In spite of morphine containing four six-member rings, none of the reported syntheses utilize a Diels-Alder reaction as a pivotal step. Although the approaches of Gates and Tius use an intermolecular Diels-Alder reaction as a step in the synthesis, neither takes full advantage of the regio and stereospecificity of the [4+2] cycloaddition. While some successful morphinan syntheses utilizing intramolecular Diels-Alder methodology have been published, this methodology has not yet been applied to a total morphine synthesis.

This dissertation describes an intramolecular Diels-Alder approach toward the construction of the nonaromatic portion of morphine **1** (B, C, D, and O rings). Through this methodology, the 5 chiral centers found in natural (-)-morphine **1** were constructed with the correct absolute stereochemistry. The stereochemical outcome of the [4+2] cycloaddition was carefully studied, and more advanced approaches to higher morphinans were designed.

CHAPTER 2
HISTORICAL

Brief History of Morphine and Morphine Syntheses

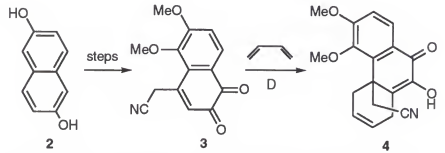
Although opium had been used for centuries, morphine was not isolated as a crystalline material until 1803 as reported by Deronse.[3] Three years later in 1806, Seguin presented a description of the isolation of morphine to the Institute of France,[4] and later that same year, Sertürner was finally credited with the first isolation of crystalline morphine.[5] In 1925, over one hundred years later, Sir Robert Robinson provided the morphine structure.[6] Finally in 1952, Gates achieved the first total synthesis of morphine[7] and thus proved the structure proposed by Robinson. In over 40 years since Gates' historic synthesis, only 16 additional total or formal syntheses have been reported in the literature. In spite of these reports and more than 150 years of effort since its discovery, a truly practical synthesis, which can compete economically with the isolation of morphine directly from the opium poppy, has not yet been achieved.

Interestingly, of the 17 total or formal syntheses of (-)-morphine to date, only two of them, the 1952 total synthesis by Gates[7] and a 1992 formal approach ending with the formation of thebainone by Tius,[8] utilize a Diels-Alder reaction in the synthesis. In both examples, an intermolecular Diels-Alder reaction is used to set up the phenanthrene core, or ABC ring system, and in neither synthesis is the Diels-Alder reaction considered a key step.

Gates' milestone synthesis of morphine in 1952 started from naphthalene diol **2**, which was subsequently converted over several steps to the substituted naphthoquinone **3**

(Scheme 1).[7] The [4+2] cycloaddition of **3** with 1,3-butadiene under thermal conditions afforded the phenanthrene **4**. Phenanthrene **4** was subjected to hydrogenation in the pre-

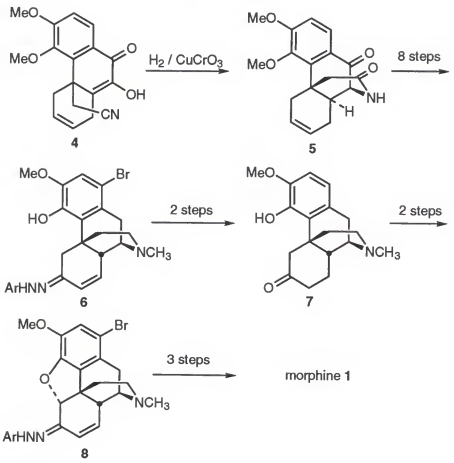
Scheme 1



2 **3** **4**

sence of copper chromite, which led to an unexpected cyclization affording tetracyclic amide **5**. Although the stereochemistry at C_9 was set correctly during the cyclization, it was necessary to epimerize the C_{14} center (Scheme 2). Gates, while attempting to close the

Scheme 2

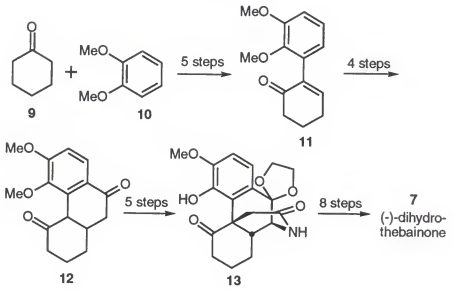


4 **5** **6** **7** **8**

furan ring via alpha bromination of the corresponding ketone, achieved this epimerization with the dinitroarylhydrazone derivative **6**. Repetition of the bromination sequence again on dihydrothebainone **7**, the most commonly intercepted intermediate in subsequent formal morphine syntheses, closed the furan ring to pentacycle **8** and completed the construction of the morphine skeleton. Finally, hydrolysis, $LiAlH_4$ reduction, and demethylation completed this first total synthesis of morphine **1**.

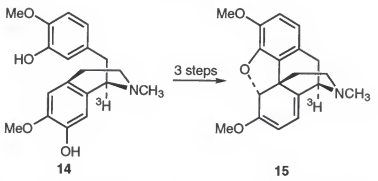
Shortly after Gates' historic total synthesis, Ginsburg completed a formal approach to morphine by synthesizing dihydrothebainone **7** in 1954.[9] Ginsburg started his approach by coupling veratrole **10** via *ortho*-lithiation with cyclohexanone **9** (Scheme 3). The coupled product was dehydrated and subsequently converted to enone **11**. Michael addition with dibenzyl malonate, followed by decarboxylation and Friedel-Crafts annulation resulted in the formation of the phenanthrenone **12**. Last, the D ring was installed after a series of steps culminating in the spontaneous formation of the ethylamine bridge accompanied by cleavage of the C_4 methyl ether and formation of tetracyclic amide **13**. An additional 8 steps followed by a d-tartaric acid resolution yielded (-)-dihydrothebainone **7** and thus, the first of many formal morphine syntheses.

Scheme 3



Nine years later, Barton presented a biomimetic synthesis of radioactive thebaine **15** (Scheme 4).[10] Starting with tritium labeled reticuline **14**, Barton performed an MnO_2 promoted oxidative coupling to construct the phenanthrene core. However, this proceeded in a very poor yield, and after two additional steps a radioisotope dilution study of the final thebaine **15** was performed to assess the 0.012% yield.

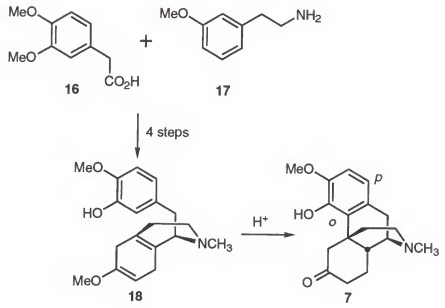
Scheme 4



14 **15**

Simultaneous reports presented in 1967 by Grewe[11] and Morrison, Waite, and Shavel[12] established a successful path for coupling the A and C rings (Scheme 5). Substituted benzyltetrahydroisoquinoline **18** was readily obtained after a Birch reduction

Scheme 5

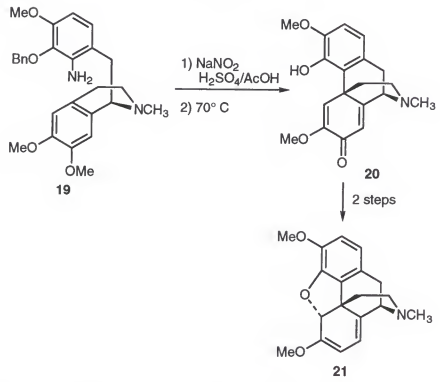


16 **17** **18** **7**

of the coupled product. Grewe then used phosphoric acid, while Morrison, Waite, and Shavel were successful with 10% aqueous HCl, to render the *ortho* coupled product in 3% yield. The *para* product was also obtained in 37% yield. The Grewe cyclization was later modified by other research groups to improve the *ortho* selectivity, and his disconnection is found in several of the following formal approaches.

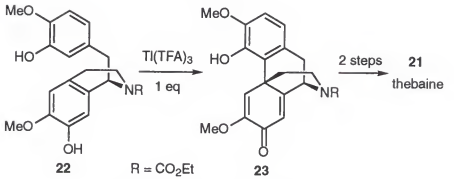
Kametani utilized a Pschorr-type cyclization in his 1969 approach to thebaine **21** (Scheme 6).[13] The cyclization of **19** to afford tetracyclic moiety **20** was achieved in a very poor yield of 1.1%, however, no *ortho-ortho* coupled products were observed.

Scheme 6



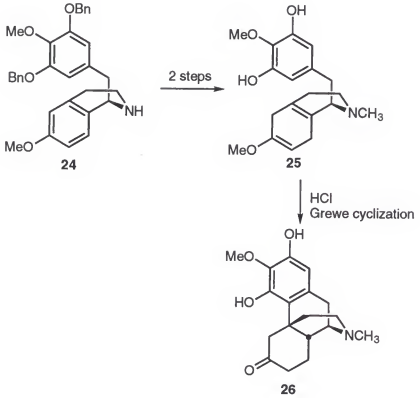
Schwartz, following a biosynthetically designed synthesis, used thallium tristrifluoroacetate to effect the *para-ortho* coupling of N-acylnorreticuline **22**, affording the corresponding salutaridine derivative **23** (Scheme 7).[14] Reduction of this intermediate with $LiAlH_4$ followed by O ring closure with HCl resulted in the formation of thebaine **21** and thus rendered the synthesis formal.

Scheme 7



Utilizing the Grewe-type cyclization, Beyerman used a symmetric arene to overcome selectivity problems.[15] N-Methylation of benzyl protected **24**, followed by hydrogenation and Birch reduction gave tricycle **25**, which readily cyclized in the presence of HCl to afford tetracycle **26** (Scheme 8). Fortunately, the additional hydroxyl group at C_2 in tetracycle **26** was selectively removed by conversion to the corresponding tetrazole

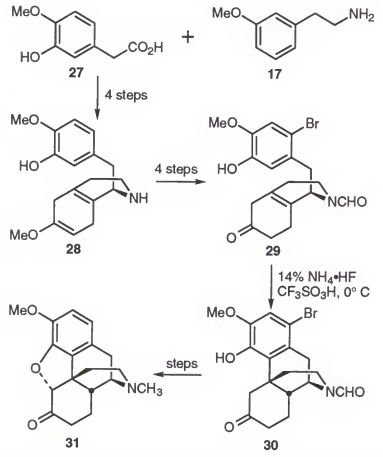
Scheme 8



ether followed by hydrogenolysis, which afforded dihydrothebainone **7** and formalized Beyerman's synthesis.

Rice is given credit for the most practical morphine synthesis to date with an overall yield of 29%.[16] Employing starting materials very similar to those of Grewe and Morrison, Rice quickly assembled amine **28** (Scheme 9). Reminiscent of Beyerman's strategy, bromine was used, to prevent tricycle **29** from undergoing *para* cyclization. Bromonordihydrothebaine **30** was formed in 60% yield, which was subsequently converted to dihydrocodeinone **31**.

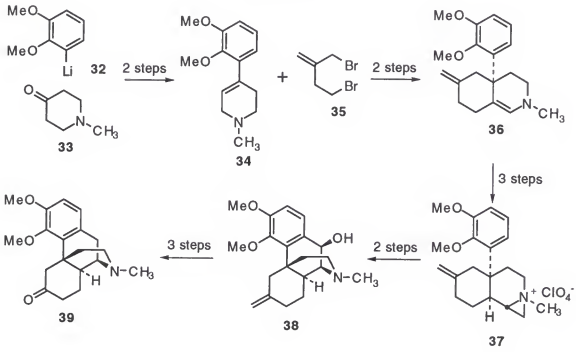
Scheme 9



In 1983 Evans utilized the *ortho* lithiated veratrole **32** in an initial coupling reaction with piperidone **33** in his formal approach (Scheme 10).[17] After the coupling, dehydration afforded alkene **34**, which was further coupled with dibromide **35**. Isoquinoline **36** was then converted to the aziridinium salt **37**, which was subsequently opened, oxidized to an

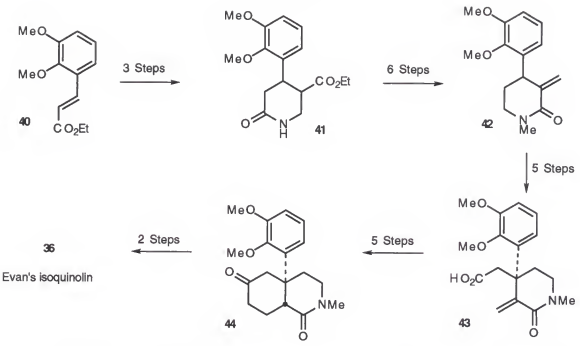
aldehyde, and finally treated with Lewis acid to form the morphinan **38**. Removal of the C_{10} hydroxyl followed by oxidation afforded ketone **39** and formalized the approach.

Scheme 10



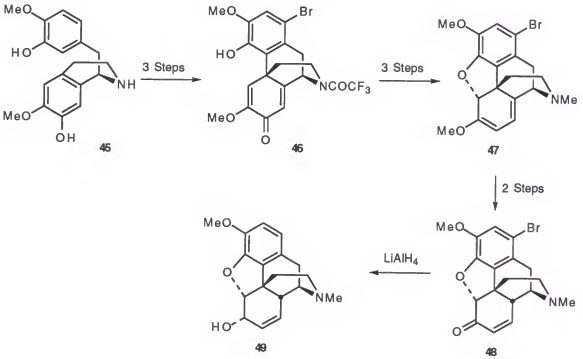
In 1983, Rapoport, after several unsuccessful attempts to finalize his approach, intercepted Evans' intermediate to formalize the synthesis (Scheme 11).[18] Construction of cinnimate **40** in 2 steps from *o*-vanillin followed by Michael addition of ethyl cyanoacetate and finally reduction and cyclization afforded lactam **41**. A benzylic oxidation, followed by an orthoester Claisen rearrangement and acid catalyzed hydrolysis, gave carboxylic acid **43**. After homologation to the β–ketoester, intramolecular Michael addition, and decarboxylation, ketone **44** was formed. Rapoport then intercepted Evans' synthesis after introduction of the methylene group.

Scheme 11



A third report in 1983 by White described an oxidative coupling approach to (-)-codiene **49** (Scheme 12).[19] (-)-Norreticuline **45**, after protection and bromination,

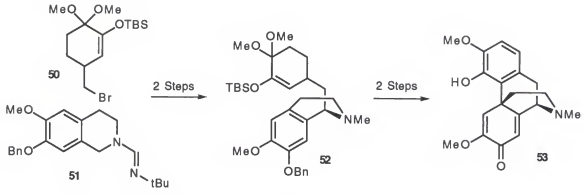
Scheme 12



underwent successful and selective *para-para* coupling to afford salutaridine analogue **46**, which was further manipulated to bromothebaine **47**. Simple hydrolysis followed by double bond migration afforded the Gates intermediate **48**, which upon treatment with $LiAlH_4$, gave (-)-codeine **49**.

In 1986, Schäfer reported another oxidative coupling formal approach to salutaridine **53** (Scheme 13).[20] Foramide **51** was coupled with bromide **50** and reductively cleaved to afford cyclization precursor **52**. Cyclization with $SnCl_4$ followed by aromatization with DDQ gave salutaridine **53**.

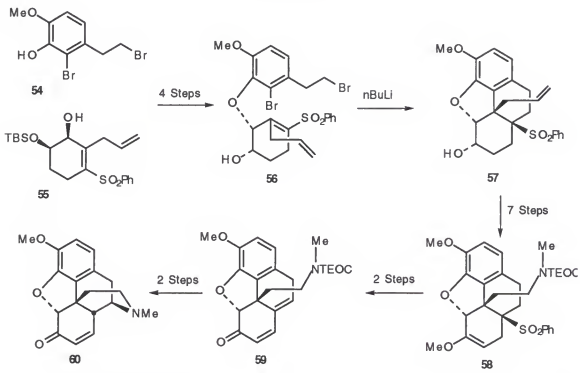
Scheme 13



In 1987, Fuchs reported a total synthesis of morphine utilizing a tandem coupling reaction to construct the morphinan skeleton.[21] Coupling of aryl **54** with alcohol **55** under Mitsunobu conditions followed by deprotection and an oxidation/reduction sequence afforded ether **56** with the desired *cis* stereochemistry (Scheme 14). The tandem cyclization was achieved by treatment of ether **56** with n-BuLi, which first closed the C_{12}-C_{13} bond and subsequently underwent alkylative closure of the final ring affording tetracycle **57**. After oxidative cleavage of the olefin to the corresponding aldehyde, the nitrogen was introduced by reductive amination and protected as the trimethylsilylethoxycarbonyl ester (TEOC) and finally oxidation followed by enolether formation afforded **58**. Base catalyzed elimination of the sulfonyl group followed by oxidation with DDQ gave dienone **59**. Upon removal of the TEOC protecting group, a 1,6-Michael type addition afforded codeinone **60**, as well as unconjugated neopinone,

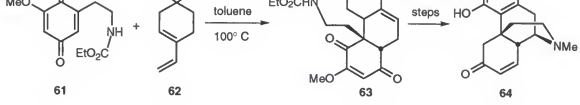
which could be readily isomerized to codeinone under the conditions reported by Rapoport and Barber.[22] Fuchs finalized his total synthesis by converting codeinone to racemic morphine **1** with reduction and demethylation.

Scheme 14



In 1992, Tius used an intermolecular Diels-Alder reaction as an early step in his formal synthesis (Scheme 15).[8] Quinone **61**, which was prepared in 7 steps from 3-methoxy-2-hydroxy benzaldehyde, was heated with diene **62**, prepared in 2 steps form 1,4-cyclohexanedione monoethlyene ketal, to rapidly construct phenanthrene **63.** After

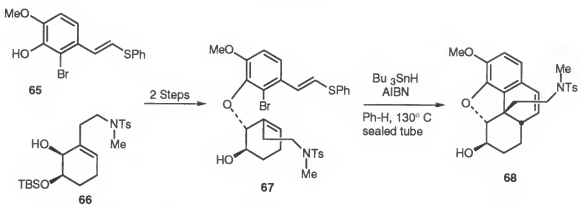
Scheme 15



several subsequent steps, Tius formalized his synthesis by constructing thebainone **64**, thus intercepting Gates'[7] approach.

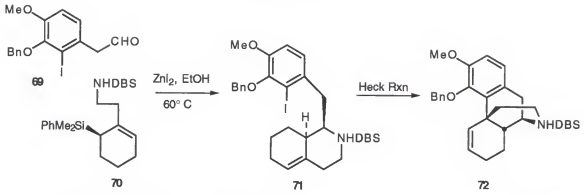
Another formal total synthesis was reported by Parker in 1993 where the key reaction involved a tandem radical cyclization to construct the morphinan skeleton.[23] Mitsunobu reaction of bromophenol **65** and *cis*-diol **66** provided the ether **67** (Scheme 16). The key cyclization proceeded via a tin mediated tandem radical cyclization to close the complete carbon skeleton of morphine giving tetracycle **68**. Following closure of the D ring, which proceeded via a nitrogen radical cyclization, Parker formalized the approach with a final oxidation step affording racemic dihydrocodeinone **31**.

Scheme 16



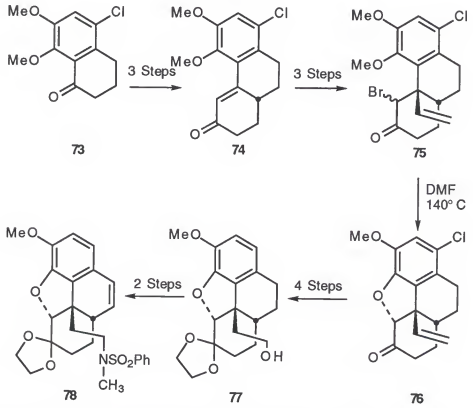
Overman published a formal synthesis of morphine in 1993, where the key step involved an intramolecular Heck reaction.[24] Chiral silane **70**, which was formed by enantioselective reduction of 2-allylcyclohexenone and subsequent steps, was condensed with aldehyde **69**, prepared from isovanillin in 7 steps (Scheme 17). The resulting coupled product **71** underwent a Heck reaction by refluxing in toluene in the presence of $Pd(OCOCF_3)_2(PPh_3)_2$ and 1,2,2,6,6-pentamethylpiperidine to give morphinan **72**. Closure of the O-ring was achieved after debenzylation, epoxidation of the olefin, and finally intramolecular attack by the phenolic hydroxyl group. Oxidation and reductive removal of the DBS (dibenzuberone) protecting group allowed Overman to formalize his approach affording (-)-dihydrocodeinone **31.**

Scheme 17



The most recent formal synthesis was published by Mulzer and coworkers in 1996 (Scheme 18).[25] The available tetralone **73** was converted by Robinson annulation to phenanthrenone **74** in 3 steps and quickly installed 14 out of 17 carbons found in the morphine skeleton The key step in the synthesis was the conjugate addition of vinyl cuprate

Scheme 18



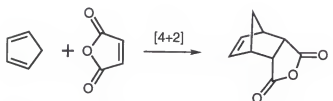
$(CH_2{=}CH_2)_2Cu\ MgCl$ to enone **74**, which established the proper stereochemistry at the quaternary benzylic center C_{13}. The enolate existing after conjugate addition was trapped

by TMSCl and further treated with N-bromosuccinimide to afforded bromide **75**. Heating the major isomer of the bromide **75** in DMF closed the O-ring affording tetracycle **76**. To begin the installation of the bridging D-ring, following ketalization, alkene **76** was subjected to hydroboration/oxidation and subsequently dechlorinated with Raney-nickel. The resulting alcohol **77** was converted to sulfonamide **78** by a Mitsunobu reaction. The synthesis was then formalized when **78** was closed to (-)-dihydrocodeinone **31** after reductive desulfonation with concomitant ring closure followed by acid catalyzed cleavage of the ketal.

The Diels-Alder Reaction

The Diels-Alder reaction, certainly one of the most widely used ring forming reactions in synthetic organic chemistry, was discovered in 1928.[26] In the original paper, the reaction of cyclopentadiene **79** and maleic anhydride **80** to afford the *endo* cycloadduct **81** was described (Scheme 19). The stereochemistry of the adduct was proven by converting the cycloadduct **81** to the known diacid. A second example, which also resulted in formation of the *endo* adduct, was the reaction of acrolein and cyclopentadiene. It was this paper, followed by a series of full papers by Otto Diels and Kurt Alder in 1929, that formally established this famous reaction, now bearing their names, and additionally earned both authors the Nobel Prize in Chemistry in 1950.

Scheme 19



79 **80** **81**

Because the Diels-Alder reaction is a concerted reaction, it is a valuable tool in synthetic chemistry. Also termed a [4 + 2] cycloaddition, the Diels-Alder reaction requires the orbital overlap of the 4 *pi* electrons of a diene with the 2 *pi* electrons of a dienophile.

The precise overlap of the reacting diene with the dienophile in the transition state renders the Diels-Alder reaction stereospecific, thus, up to 4 chiral centers can be formed simultaneously. Substitution on either the diene or the dienophile allows for regiocontrol of the cyclization process. The reaction also tolerates a wide variety of substituents on either the diene or dienophile and has been extensively utilized by the synthetic community for the design and synthesis of natural products containing 6 member rings.[27]

The Diels-Alder reaction may be further classified into three types of cycloadditions: 1) normal Diels-Alder reactions or $HOMO_{diene}$-controlled; 2) the neutral Diels-Alder reaction; 3) and the inverse demand or $LUMO_{diene}$-controlled (Figure 1). The majority of studies involving Diels-Alder reactions have been of the normal or $HOMO_{diene}$-controlled subclass. When an electron-rich diene system reacts with an electron-deficient dienophile, the reaction is much more facile than in the neutral case since these substituents lower the energy gap between the $HOMO_{diene}$ and $LUMO_{dienophile}$. This is also true in the inverse demand case with the exception that the $LUMO_{diene}$ is lowered by the electron withdrawing group and the $HOMO_{dienophile}$ is raised by the electron donating group.

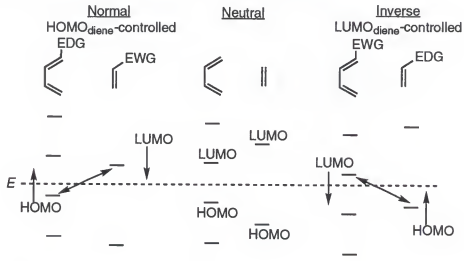


Figure 1. Types of Diels-Alder reactions

The mechanism of the Diels-Alder reaction is believed to be a concerted process where the two new bonds are formed both simultaneously and stereospecifically. A common method for describing the mechanism of a Diels-Alder reaction is through Frontier

Molecular Orbital Theory. R. B. Woodward and R. Hoffmann first used molecular orbital theory to explain the pattern of reactivity in pericyclic reactions in their book The Conservation of Orbital Symmetry.[28] According to the Woodward-Hoffmann rules, the Diels-Alder reaction is a concerted, symmetry-allowed $[_{\pi}4_s + _{\pi}2_s]$ process. The orbital overlap between the highest-occupied molecular orbital (HOMO) of the diene and the lowest-unoccupied molecular orbital (LUMO) of the dienophile are such that only bonding interactions result in the transition state. Closer inspection of this model indicates that the overlap of the diene and dienophile orbitals would therefore be suprafacial with respect to one another, thus resulting in a stereospecific *syn* addition. Of course, the diene must be capable of adopting an *s-cis* configuration for this transition state to be possible.

Additionally, the *endo* versus *exo* stereochemistry of Diels-Alder products can be explained by FMO theory. It is a general observation that if a dienophile contains frontier orbitals that are not directly involved in the cycloaddition, these orbitals will prefer to overlap with the diene in the transition state. This secondary orbital overlap, experimentally known as the Alder rule, leads to the formation of the *endo* product under kinetically controlled conditions. Even though secondary orbital overlap does not directly lead to bond formation, it does significantly lower the energy in the transition state and is therefore preferred over the *exo* transition state.[29]

Frontier Molecular Orbital Theory can also be used to describe the regiochemical control inherent in the Diels-Alder reaction. In a normal Diels-Alder reaction between an electron-rich diene and an electron-deficient dienophile, the diene is substituted with an electron-donating group at C_1. In this situation, FMO calculations show that the largest atomic coefficient is at C_4. Additionally, on the dienophile, which is substituted with an electron withdrawing group, the largest atomic coefficient is at C_2. FMO theory would then predict that C_4 of the diene would overlap best with C_2 of the dienophile in the transition state, thus resulting in the formation of the *ortho* cycloadduct. In a second normal Diels-Alder case where this time the C_2 of the diene is substituted with the electron

donating group, the largest atomic coefficient would be at C_1, thus resulting in the formation of the *para* substituted product. Therefore, by altering the substitution pattern of either the diene or the dienophile, regiocontrol in the cycloaddition can be achieved.

The Intramolecular Diels-Alder Reaction

General Concepts

Quite surprisingly, the intramolecular version of the Diels-Alder reaction was not reported until 1953.[30] The initial report by Alder and Schumaker was followed by isolated examples, which were published almost 10 years later.[31] Since that time, a wealth of intramolecular cycloadditions have been reported as evidenced by several reviews.[32] The major advantage of the intramolecular reaction is that fused two-ring systems are formed in a single chemical step, although bridged ring systems have also been synthesized. The size of the two-ring system is controlled by the length of the tether between the diene and the dienophile. Additionally, because the diene and the dieneophile are built into the same molecule, full regio and pronounced stereocontrol are typical features of the reaction. These qualities make the intramolecular Diels-Alder (IMDA) reaction especially useful in the design of syntheses for molecules containing stereospecifically fused 5,6 or 6,6 ring systems.

The intramolecular Diels-Alder reaction can be subdivided into two classes that are based on the configuration of the starting triene. For Type I terminally tethered systems, successful reactions result in the formation of fused-ring systems, even in the case of (*Z*)-dienes. Bridged products for trienes containing three or four atom tethers are not observed because the transition state leading to these products is too highly strained. Noteworthy of Type I IMDA reactions is that the cyclization of (*E*)-dienes results in the formation of either *cis* or *trans*-fused cycloadducts, while cyclization of (*Z*)-dienes yields only *cis* adducts (Figure 2). Type II internally tethered trienes are used when bridged cycloadducts are

preferred. Additionally, as first noted by Shea in 1982,[33] Type II trienes with three and four atom tethers lead exclusively to the *syn* bridged cycloadduct.

The first intramolecular Diels-Alder study dealing with Type I triene systems was reported by House in 1965.[34] House, working entirely with all carbon nonatriene systems,

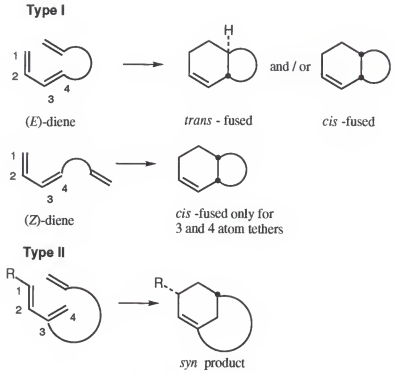
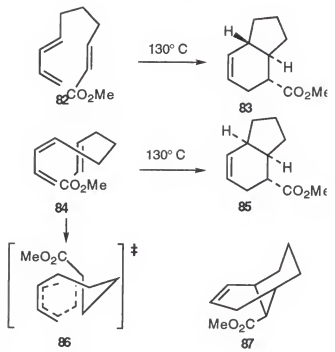


Figure 2. Types of intramolecular Diels-Alder reactions

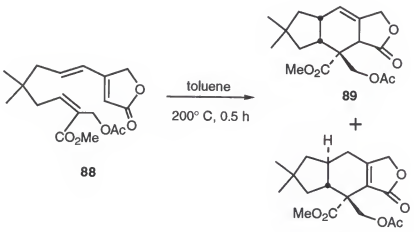
reported that fused-ring systems are attainable in the cases where tethers of 3 or more atoms were used. The majority of these reactions resulted in the formation of fused-ring systems that were single structural stereoisomers (Scheme 20). House further noted that a Type I (Z)-diene **84** yielded only the *cis* product **85** because the transition state leading to the *trans* product was too highly strained. Most importantly, House concluded this report by stating "the structural orientation observed in our intramolecular reactions correspond to the minor product produced in an analogous intermolecular reaction."

Scheme 20



In 1980 Boeckman, while pursuing the total synthesis of (±)-marasmic acid, first addressed the questions regarding stereocontrol of the intramolecular Diels-Alder reaction.[35] The crucial cyclization of dienone **88** resulted in a 1:1 mixture of the *cis* **89** to *trans* **90** cycloadducts (Scheme 21). This result showed that the Alder *endo* rule was not

Scheme 21

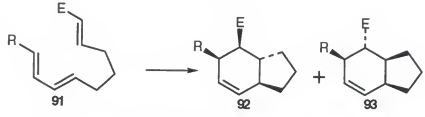


the primary influence in the outcome of IMDA reactions, clearly differentiated from the bimolecular case. Boeckman suggested that an alternative model for describing the transition state had to be developed since "secondary orbital interactions are energetically insufficien t to overcome nonbonding interactions in the transition state leading to the *cis*isomer." This example, along with the preference for the production of *trans* hydrindenes reported by Roush in 1979,[36] suggested that nonbonding interactions and conformational preferences of the tether cause the triene to adopt an unsymmetrical transition state. This paper, along with the previous report by House, prompted several research groups to undertake further mechanistic investigations.

The mechanism of the intramolecular Diels-Alder reaction is believed to be a concerted but asynchronous $[_{\pi}4_{s} + _{\pi}2_{s}]$ process, whereby stereo and regiochemistry are established strictly in the transition state. Following the work of House, a series of examples of non-activated and activated nonatriene systems appeared in the literature and addressed the electronic considerations involved in the mechanism of IMDA reactions. Comparison of these three differently activated systems demonstrates how diastereoselection is determined in the transition state.

In 1982, Roush and coworkers published an early study on diastereoselection with terminally activated nonatriene systems (Scheme 22).[37] Both (*Z*) and (*E*) activated

Scheme 22



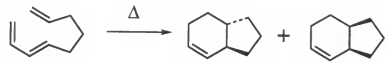
E = CO_2Me	150° C, 40 h, 65%	60	to	40
R = H	150° C, 40 h, 72%	72	to	28
R = iPr				

dienophiles of triene **91** formed the *trans* cycloadduct preferentially. This investigation displayed the failure of the Alder *endo* rule in predicting the outcome of the IMDA

cyclizations and also showed that the outcome was independent of dienophile stereochemistry. Interestingly, when the Lewis acid catalyst $MeOAlCl_2$ was used in the cyclization of isopropyl substituted triene **91**, the *trans* adduct formed exclusively.

A second case was reported a few years later by Houk and coworkers when they studied the trends of stereoselectivity for unactivated nonatrienes.[38] An unsubstituted 1,3,8-nonatriene **94** was heated at varying temperatures and times (Scheme 23). While increased temperatures improved the yield of the reaction, the product ratio was not significantly affected, and in each case the *cis* isomer **96** formed preferentially to the *trans* isomer **95** (70:30). This observation contrasted with the findings of Roush for the terminally substituted case. There was also a 1 kcal/mol preference for the *cis* adduct. Thus, in the unsubstituted case, the thermodynamically preferred *endo* adduct was obtained.

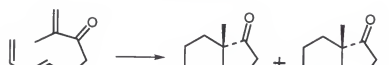
Scheme 23



94 **95** **96**

Third, in 1975, Bajorek and Sutherland reported that thermal cyclization of substituted trienone **97** yielded only the *cis*-fused adduct.[39] The product ratios of this system were later investigated more thoroughly by Jung in 1981.[40] In this paper, the internally activated nonatriene **97** was reported to show moderate *cis* stereoselectivity to afford a 30:70 mixture of bicycles **98** and **99** (Scheme 24).

Scheme 24



97 **98** **99**

The trend for *cis* stereoselectivity led Houk to perform an additional model study that introduced the concept of "twist-asynchronicity" as a method for describing the stereochemical outcome of IMDA cyclizations.[41] The model suggested that stereochemistry is controlled by the timing of the bond formation in the transition state (Figure 3). When an activating group W is placed on the terminal end of the dienophile, the bond is polarized so that the LUMO coefficient at C_2 is larger than at C_1. FMO theory suggests that the bonding between C_2 and C_6 would be slightly more advanced in the transition state than that between C_1 and C_9 because of enhanced matching of the coefficients. The match between C_2 and C_6 causes the triene to torque or twist in the transition state and shows asynchronous enhancement of bond formation. But, in the internally activated system, the trend is reversed. The LUMO coefficient at C_1 is greater than at C_2, therefore the C_1-C_9 bond is more advanced in the transition state. The twist property in the transition state of internally activated nonatrienes is therefore not as significant because Houk previously demonstrated that the selectivities in this instance match those for the unsubstituted cases.[42]

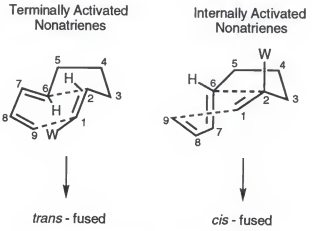
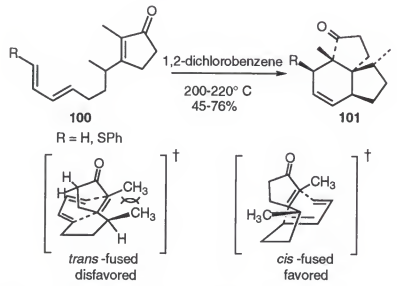


Figure 3. Houk's Twist-asychronicity model

Of additional interest are the steric effects in the transition state of intramolecular Diels-Alder reactions because they have more of an influence on the stereochemical outcome of the reaction than the electronic effects. An example was reported by the Kametani group in 1987 in their stereoselective total synthesis of the angular tricyclopentanoid sesquiterpene (±)-3-oxosilphinene (Scheme 25).[43] A terminally activated

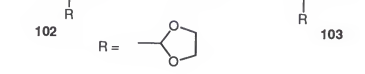
cyclic dienophile **100** cyclized exclusively to the *cis* isomer **101**. The offered explanation was based on the steric interactions that take place in each of the respective transition states. Because of unfavorable steric interactions between the cyclopentane ring and the diene as well as between the two methyl groups in the *endo* transition state, the only observed product was the *exo* adduct tricycle **101**.

Scheme 25



An important second example of this effect, which demonstrated an opposite stereochemical outcome from that predicted in Houk's "twist-asynchronicity" model for an internally activated nonatriene system, was reported by Craig, Ley and coworkers in 1988 (Scheme 26).[44] Because of the large size of the R group at C_7 in the triene **102**, an unfavorable interaction results and prevents the molecule from assuming the *cis*-like transi-

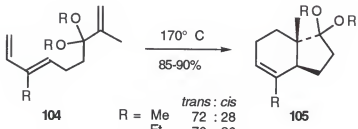
Scheme 26



transition state. Therefore, the *trans* isomer **103** again is the only observed adduct.

Finally, an earlier example of similar steric influences was presented by Jung in 1981 as the cyclization of ketal **104** was investigated (Scheme 27).[40] If electronic effects were solely responsible for the formation of products, Houk's "twist-asynchronicity" model would have predicted the *cis* isomer to be the major product for this unactivated dienophile. However, here the steric interaction between the ketal and the diene in the transition state again reverses the ratio.

Scheme 27



104 R = Me Et *trans* : *cis* 72 : 28 70 : 30 **105**

With competing electronic and steric effects, predicting the stereochemical outcome of IMDA reactions is indeed difficult. Given the previous examples, manipulation of the diene or dienophile accordingly can lead to the desired cycloadducts. However, ultimately product ratios are determined experimentally and vary with each substrate.

Survey of Experimental Conditions

Successful intramolecular Diels-Alder reactions, like their intermolecular counterparts, can be achieved through a variety of conditions. The use of thermal energy to induce cycloaddition is the primary method, the severity of which is dependent on the substituents. A second technique utilizes Lewis acids or Bronsted acids. In unactivated systems, catalysis by acids or transition metals has also been applied to intramolecular Diels-Alder reactions. Studies of Diels-Alder reactions in aqueous media have also been conducted. Finally, more nonconventional techniques such as high pressure, microwave radiation, and sonication have been used for Diels-Alder reactions.

Thermal conditions

The most common method for performing intramolecular Diels-Alder cycloadditions is under thermal reaction conditions. Examples of thermal [4+2] cycloadditions resulting in fused 5,6-ring systems are extremely abundant in the literature. A few representative examples shown in Table 1 demonstrate the variation in the temperatures necessary to facilitate certain IMDA reactions. The temperature requirements are dependent upon the substituents on the nonatriene system and are difficult to predict except through experimentation.

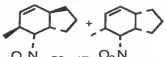
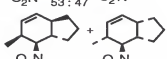
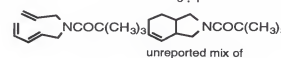
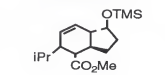
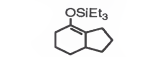
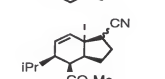
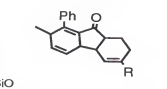
Triene	Product	° C / Time	Yield	Ref.
		23 / 84 h	74 %	45
		80 / 30 h	64 %	45
 unreported mix of *cis : trans* isomers		90-95 / not reported	88 %	46
		110 / 85 h	72.5%	47
		160 / not reported	55 %	48
		180 / 3 days	49 %	49
		240 / 3 - 5 h	30 %	50

Table 1. Thermal Intramolecular Diels-Alder Reactions

Lewis acid catalysis

Another common method for performing intramolecular Diels-Alder reactions is through the use of Lewis acid catalysis, which generally affords the cycloadducts under much milder conditions and at accelerated rates. The rate acceleration was first observed by Yates and Eaton in 1960 while studying the intermolecular Diels-Alder reactions of maleic anhydride, dimethylfumarate, and *p*-benzoquinone with anthracene.[51] Later in a paper by Houk, it was reported that when a protic or Lewis acid coordinates to a carbonyl oxygen of an activated dienophile, the dienophile's π system is polarized and the values of the coefficients are altered.[52] In the case of acrolein, as seen in the frontier orbital energy diagram below (Figure 4), where energies are reported in (eV), coordination of a proton to the carbonyl significantly lowers the LUMO energy of the dienophile component. This lowering of the energy gap explains the reason for accelerated rates of cycloaddition when acids are used to catalyze Diels-Alder reactions. Houk further described that, since the coefficients are also affected during Lewis acid catalysis, enhancements in regioselectivity are observed.

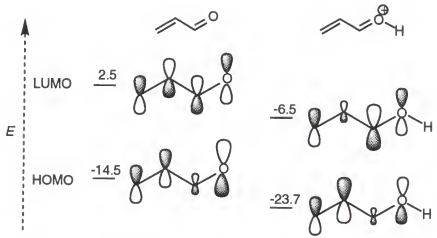
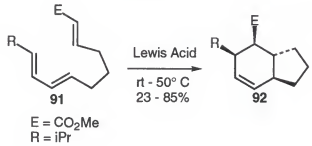


Figure 4. Effect of acid on HOMO and LUMO energies

As eluded to in the previous section, Roush was the first to publish a complete study on Lewis acid catalysis of IMDA reactions[37] that clearly demonstrated the benefits.

When the terminally activated triene **91** was reacted with a variety of Lewis acids, including $MeOAlCl_2$, $EtAlCl_2$, $AlCl_3$, $BF_3{\bullet}Et_2O$, $TiCl_4$, $SnCl_4$, WCl_6, and $NbCl_5$, only the *trans* adduct **92** was isolated (Scheme 28). When compared to the thermal conditions, which showed formation of a product mixture and required high temperatures and long reaction times, the benefits of Lewis acid catalysis are readily apparent.

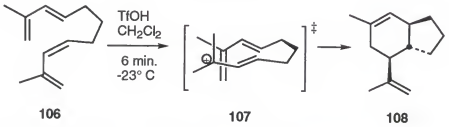
Scheme 28



Protic acid catalysis

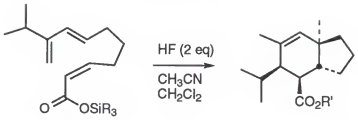
Another method of catalyzing IMDA reactions invokes the use of simple Bronsted acids. An early example was published by Gassman in 1984 when tetraene **106** underwent rapid cyclization via the tertiary allylic carbocation **107** exclusively to the *trans* adduct **108** (Scheme 29).[53]

Scheme 29



Roush also invoked a cationic transition state to explain the formation of the *trans*-fused product **110** in the hydrofluoric acid catalyzed cyclization of terminally activated triene **109** (Scheme 30).[54] The first equivalent of HF cleaved the silyl protecting group, while the second promoted the formation of the 1,3-dioxolenium cation, which directed the subsequent *endo* ring closure to the *trans*-fused bicycle **110**.

Scheme 30

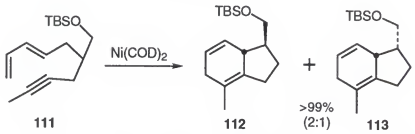


109 **110**

Transition metal catalysis

The use of transition metals to catalyze IMDA reactions is of particular interest with unactivated or neutral triene systems. Unlike Lewis acids, transition metals coordinate directly to the *pi* system of trienes and bring the diene and dienophile together resulting in cycloadditions under very mild conditions. The first transition-metal catalyzed IMDA reaction was in 1989 when Wender reported the nickel (0) catalyzed reaction of dienyne **111** efficiently to 1,4-cyclohexadienes **112** and **113** (Scheme 31).[55] In contrast, when dienyne **111** was cyclized without a catalyst present, temperatures greater than 160° C were required.

Scheme 31

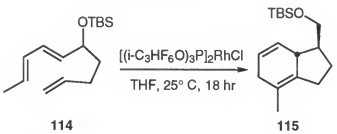


111 **112** **113**

Shortly after Wender's communication, Livinghouse reported the use of rhodium(I) catalysis to cyclize similar dienynes. More interestingly was the cyclization of triene **114**, which efficiently afforded the 5,6-bicyclic **115** (Scheme 32).[56] This example demonstrated that rhodium(I) catalysis could be used to cyclize trienes that contained a terminal alkene. Although the overall yield of the cyclization was lower than that of Wender's, the exclusive

formation of one cycloadduct demonstrated the excellent diastereoselectivity of rhodium(I) catalysis.

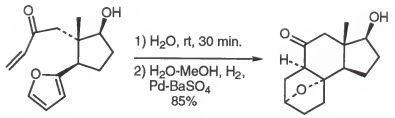
Scheme 32



Aqueous conditions

Studies of water promoted Diels-Alder reactions have also recently appeared in the literature.[57] In 1980, Breslow reported that Diels-Alder reactions between cyclopentadiene and butenone, when performed in aqueous solutions, showed significant rate acceleration.[58] The acceleration was attributed to the "hydrophobic effect," which results as the nonpolar molecules aggregate in order to diminish the hydrocarbon-water interfacial area. Breslow additionally reported that the rate increased even more so when LiCl was added to the solution, which caused the nonpolar material to "salt out" of solution, further enhancing aggregation. A final important result reported by Breslow was that β-cyclodextrin provided a cavity where the diene and the dienophile could aggregate, causing marked increases in the Diels-Alder cycloaddition rate. Although the majority of the reported reactions were bimolecular, an example involving an intramolecular Diels-Alder reaction in water was published in 1985 by DeClercq when the furan **116** cyclized spontaneously at room temperature in water to give tetracycle **117** (Scheme 33).[59] The aqueous solvent provided good yields and rapid reactions under very mild conditions.

Scheme 33

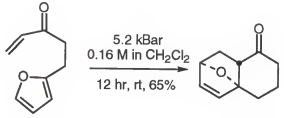


116 **117**

High pressure

The use of high pressure in organic synthesis is well documented and has also been successfully applied to Diels-Alder cycloadditions.[60] High pressure is especially useful for reactions where large negative activation volumes exist, and increased pressure leads to increased reaction rates. Dauben and Krabbenhoft first reported high-pressure intermolecular Diels-Alder reactions in 1976.[61] Interestingly, relatively few IMDA reactions using high pressure have been reported; however, those that have contain a furan unit as the diene.[62] A more recent example by Keay demonstrated the facile high pressure cyclization of furan **118** to afford exclusively *exo* adduct **119** (Scheme 34).[63] The use of high pressure readily shifted the unfavorable equilibrium toward the product. Since furan

Scheme 34



118 **119**

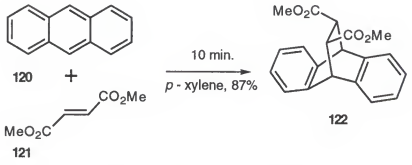
dienes are aromatic, the equilibrium of IMDA reactions tend to favor the starting materials over the products. Thus, cyclization of furan dienes under standard thermal conditions[64] and through the use of β-cyclodextrins[65] or reactions in aqueous solutions[66] proved to be very difficult.

Unconventional techniques

More unconventional techniques such as microwave radiation and sonication have also been applied to Diels-Alder reactions. The use of microwave ovens for conducting organic reactions was first reported in 1986.[67] The principle advantage of microwave heating is that it greatly increases reaction rates. An example of this was demonstrated for the intermolecular Diels-Alder reaction between anthracene **120** and activated diester **121** (Scheme 35). In contrast, the identical reaction required heating for 72 hours in refluxing dioxane.[68] To date, no examples of intramolecular Diels-Alder cycloadditions promoted by microwave radiation have been reported.

Similarly, sonication has been successfully applied to intermolecular Diels-Alder reactions. The technique of ultrasound uses frequencies ranging from 20 kHz to 10 Mhz. When a reaction is exposed to ultrasound, acoustic cavitation results in the formation of small bubbles. As the bubbles collapse, localized temperatures of 5200 K within the cavity have been measured by Suslick[69] and pressures of 1000 atmospheres have been estimated. Understandably, these tremendous localized temperatures and pressures can cause significant rate enhancements of chemical reactions.

Scheme 35



The first ultrasound promoted bimolecular Diels-Alder reaction of quinone with various dienes was reported by Lee and Snyder in 1989.[70] A very recent report by Caulier and Reisse[71] discussed the sonochemical effects of the reaction of cyclopentadiene with methyl vinyl ketone in chlorinated solvents. Interestingly, this paper points out that it is not

the high temperature and pressures resulting from cavitation collapse, but rather the production of HCl which ultimately causes the rate enhancement. The application of sonication to Diels-Alder reactions is in its infancy and no examples for IMDA reactions have been reported.

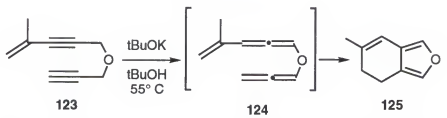
Three Atom Tethered IMDA Reactions Containing a Central Oxygen

Of particular interest to the topic of this dissertation are the previous examples of intramolecular Diels-Alder reactions of systems containing a central oxygen atom in the tether. Both ether and ester tethered systems have been reported in the literature, but examples with unactivated dienophiles are scarcely found. The majority of the successful reactions were conducted under thermal conditions, however in the case of unactivated ether tethered systems, base and transition metal catalysis proved to be more efficient.

Ether Tethers

One of the earliest ether tethered IMDA reactions was reported in 1974 by Bartlett.[72] Initial base catalyzed isomerization of the starting ether **123** to the corresponding allene **124** was followed by an IMDA reaction to afford a bicyclic product which readily isomerized at room temperature to dihydroisobenzofuran **125** (Scheme 36). In addition to proving the presence of the allene intermediate, this paper set a precedent for ether tethered IMDA reactions.

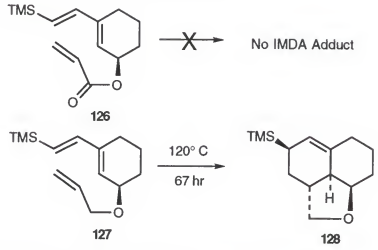
Scheme 36



In 1983, while targeting the total synthesis of nagilactones, Burke[73] and coworkers successfully cyclized ether tethered triene systems. After discovering that acrylate **126** was rather unstable and gave only elimination and polymerization products under both

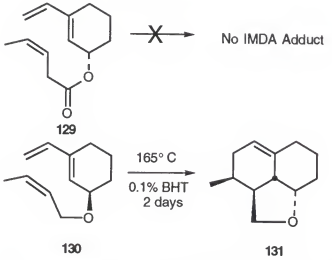
thermal and Lewis acid catalyzed conditions, the more simple ether model was studied (Scheme 37). In contrast, when the triene **127** was subjected to 120° C for 67 hours, the tricyclic adduct **128** was isolated in good yield.

Scheme 37



One year later, a structurally similar ether tethered system was cyclized by Funk and coworkers while developing a Diels-Alder strategy for synthesizing compactin (Scheme 38).[74] Funk encountered problems similar to those previously reported by Boeckman

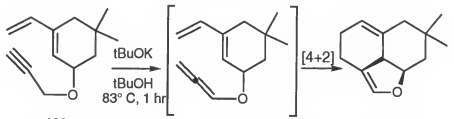
Scheme 38



when the ester-tethered triene **129** failed to cyclize to the desired lactone. Subsequently, a less labile etherlinkage was utilized. The ether tethered triene **130**, easily cyclized preferentially (4:1) to the *exo* tetrahydrofuran moiety **131**.

Further efforts by Kanematsu[75] and coworkers toward the synthesis of tricyclic lactones in 1986, showed the use of Bartlett's[72] previously discussed base catalyzed IMDA method (Scheme 39). The ease of cyclization of ether **132** was attributed to the favorable

Scheme 39

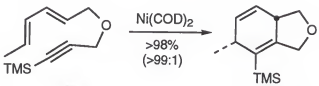


132 **133** **134**

geometry of the allenyl intermediate **133**. Facile and stereospecific cyclization under mild basic conditions afforded tricycle **134** in excellent yield.

More recently, Wender and Livinghouse independently reported the use of transition metals as templates for intramolecular Diels-Alder reactions of ether tethered systems. Wender successfully cyclized dienynes via a nickel-catalyzed reaction.[55] Ether **135** was cyclized with excellent yield and selectivity to the corresponding bicyclic isobenzofuran **136** (Scheme 40). This mild and efficient [4+2] cycloaddition provided a practical method for cyclizing otherwise unactivated dienyne systems.

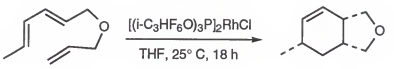
Scheme 40



135 136

Livinghouse conducted analogous rhodium catalyzed intramolecular Diels-Alder cycloadditions.[56] However, with rhodium catalysis, the reactions were not limited to terminal alkynes. Thus, terminal alkene **137** cyclized just as readily in excellent yield to the fused 5,6-ring system **138** (Scheme 41).

Scheme 41

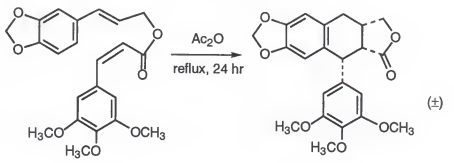


137 **138**

Ester Tethers

One of the first oxygen tethered IMDA reactions was reported in 1966 by Klemm and coworkers as a key step in their approach to synthetic lignan lactones.[76] The open-chain unsaturated *trans,cis*-dienoic ester **139** was heated in acetic anhydride and successfully cyclized to racemic isodesoxypicropodophyllin **140** (Scheme 42).

Scheme 42

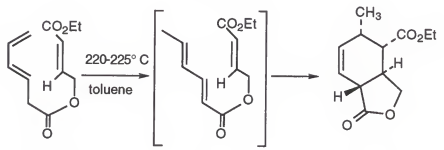


139 **140**

A second early ester tethered IMDA reaction was reported by Boeckman as part of a synthetic approach to δ-lactones related to vernolepin.[77] Several significant facts regarding heteroatom tethered IMDA reactions were revealed. An attempt to cyclize ester **141** under thermal conditions in a sealed tube, surprisingly lead to an 8 to 1 mixture of the *trans* to *cis* fused γ–lactone **143** (Scheme 43). The adduct formed only after the diene system isomerized to the fully conjugated intermediate **142**. Importantly, Boeckman concluded that the electronic requirements of the ester were more significant than any steric concerns, since esters nearly totally exist in a transoid geometry. Thus, in the unconjugated form, the diene and dieneophile were never able to adopt the configuration necessary for the

cycloaddition to occur. However, once the isomerization occurred, ester **142** was no longer prevented from reaching the appropriate transition state geometry. The overlap requirements of the heteroatoms was further examined when two derivatives of **141**, the

Scheme 43

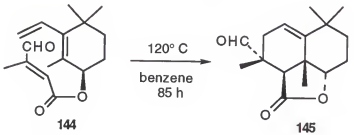


141 **142** **143**

the first where the oxygen was replaced with a methylene and the second where the ketone was similarly replaced, cyclized readily to the expected 6,6-fused ring systems. It was finally concluded that the location of heteroatoms in the tether of the triene, as first suggested by Oppolzer,[78] and their overlap requirements have a dramatic affect on both the rate of reaction and product distribution of the intramolecular cycloaddition.

Continuing interest in the use of ester tethered IMDA reactions for the construction of tricyclic lactones was reported in 1985 by Ziegler and coworkers in an approach to forskolin intermediates (Scheme 44).[79] Cognizant of the difficulties previously encountered by Burke,[73] Ziegler incorporated a terminal aldehyde to both activate and stabilize triene **144** as well as assist in directing the cycloaddition to the desired *endo* tricyclic lactone **145**.

Scheme 44



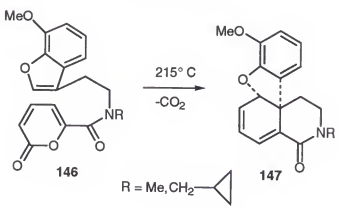
144 **145**

Approaches to Morphinans Utilizing an Intramolecular Diels-Alder Methodology

Inspection of the 17 current synthetic approaches to morphine reveals that, while the Diels-Alder reaction has been used as an efficient step in the syntheses of Gates and Tius, not one has incorporated an intramolecular Diels-Alder methodology. However, there have been a few reports in the literature which demonstrate the utility of the IMDA reaction in forming morphinans. These reports support the fact that IMDA methodology is a valid means for synthesizing morphinans, and therefore suggest the necessity for further investigation and application of this methodology toward a total morphine synthesis.

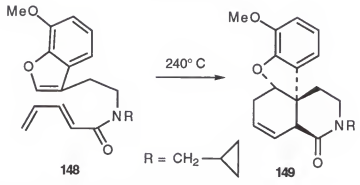
In 1981, Ciganek was first to report the synthesis of a new morphine fragment via the intramolecular Diels-Alder reaction.[80] The key [4+2] cycloaddition occurred when N-(7-methoxy-3-benzofuranethyl)-N-methyl-6α-pyrone-carboxamide **146** was subjected to heating in refluxing solvent for several hours to afford lactam **147** (Scheme 45). The driving force for this cycloaddition was the chelotropic extrusion of carbon dioxide which trapped the cycloadduct and prevented reversion to the starting material. Following hydrogenation of the diene, reduction of the amide ketone and demethylation of the R = cyclopropylmethyl analogue, the absolute configuration of the cycloadduct was assigned by single growth X-ray structure determination. This communication was also the first published example of a successful Diels-Alder reaction of a benzofuran dienophile.

Scheme 45



Ciganek reported a second tethered system **148** which was also successfully cyclized under analogous thermal conditions to tetracyclic lactam **149** (Scheme 46). Interesting to note here is that in the second example Ciganek isolated only the *cis* isomer

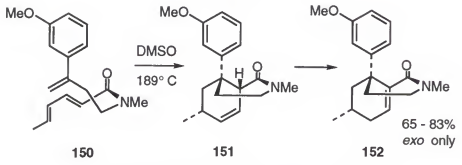
Scheme 46



after following the same derivitization as described in the first example. Both of these reactions utilized the intramolecular Diels-Alder methodology to properly construct four of morphine's five rings.

Four years later in 1985, Jones reported the intramolecular Diels-Alder reaction of an (*E,E*)-aryl triene **150** which was readily obtained in three steps from the corresponding acrylophenone (Scheme 47).[81] Under thermal conditions, triene **150** was successfully

Scheme 47

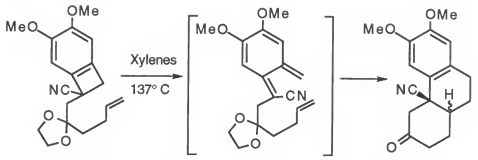


cyclized and subsequently converted to a morphine fragment. In this communication, the IMDA reaction was used to stereospecifically form 4α-aryloctahydroisoquinoline **152**. The initially formed Diels-Alder adduct **151** underwent facile isomerization to the α,β-unsaturated bicyclic lactam **152**. Finally, hydrogenation of the lactam **152** followed by

reduction afforded the corresponding amine which was known to be biologically active.

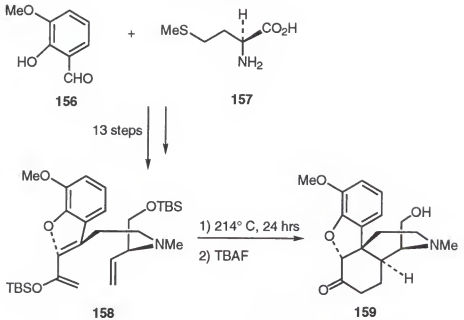
One year following Jones' report, Kametani reported the successful IMDA thermal cyclization of a benzocyclobutene derivative **153** providing tricyclic compound **155** in which the major product contained the correct *cis* B/C ring junction found in natural morphine (Scheme 48).[82] Most important to note is that in this single step Kametani set the proper C_{13} and C_{14} stereochemistry for morphine, and was also able to further manipulate **155** in subsequent chemical steps to properly close the D ring onto the established phenanthrene core.

Scheme 48



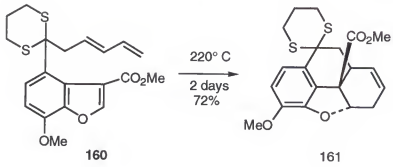
In 1988, Constanzo and Dalton reported another intramolecular Diels-Alder approach to morphine (Scheme 49).[83] Constanzo's convergent approach started with *ortho* vanillin, **156** and (*S*)-(+)-methionine, **157**, which were converted in 13 steps to the immediate IMDA precursor, **158**. Under thermal conditions the desired cyclization occurred and the A, C, D and O rings of the morphine skeleton in tetracyclic **159** were established. The IMDA reaction proved to be the key step in the synthesis, but unfortunately because of an extremely poor yield, the final C_{10}-C_{11} closure was not achieved.

Scheme 49



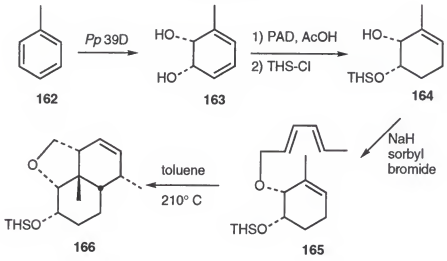
In 1990, Wu and Stork reported an intramolecular Diels-Alder strategy in the simultaneous construction of the B and C rings of morphine.[84] Wu followed an approach similar to that of Ciganek by utilizing benzofuran as the dienophile. Additionally, Wu used a geminal dithiane to assist the IMDA reaction through a Thorpe-Ingold effect. The most successful cyclization was when benzofuran **160** was heated to afford the tetracycle **161** in good yield (Scheme 50). The ester of the tetracycle **161** was reduced with DIBAL to afford a 3 to 1 mixture of the primary alcohol and aldehyde, however installation of the nitrogen and subsequent closure of the D ring was not reported.

Scheme 50



In 1992, the Hudlicky research group published an initial intramolecular Diels-Alder model study directed toward a total synthesis of morphine.[85] The *cis*-dienediol **163** derived from microbial dihydroxylation of toluene was converted to the tricycle **166** in 5 steps (Scheme 51). By taking advantage of the stereospecificity of the biooxidation, the ether tethered diene was readily delivered from the α face of the molecule in the key IMDA cyclization. The biooxidation correctly set the stereocenters at C_4 and C_5 while the IMDA step properly set those at C_{13} and C_{14}. This example demonstrated an efficient approach to an interesting morphine fragment and provided the basis from which the subsequent second generation Diels-Alder model study evolved.

Scheme 51



162 **163** **164** **165** **166**

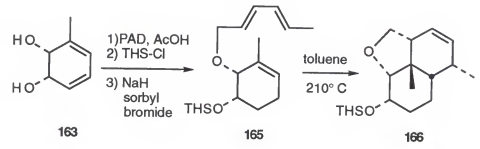
CHAPTER 3
RESULTS AND DISCUSSION

Introduction

While the intramolecular Diels-Alder strategy has been applied in approaches to a variety of morphinans, a successful completion of a total synthesis of natural (-)-morphine by this technique has not been reported. In this advanced model study, a chemoenzymatic approach to the construction of the five chiral centers of (-)-morphine with the key step being an intramolecular [4+2] cycloaddition is described. While two chiral centers (C_5 and C_6) are set during the initial enzymatic dihydroxylation, the remaining three centers (C_9, C_{13}, and C_{14}) are set simultaneously in an intramolecular Diels-Alder cycloaddition. This strategy provides a methodology which can be further expanded in the pursuit of a total synthesis of (-)-morphine.

In 1992, the Hudlicky research group reported a first generation intramolecular Diels-Alder model study toward the synthesis of morphine.[85] The reported cycloadduct **166** (*sic*), the assumed product of *endo* cyclization, was obtained under thermal Diels-Alder conditions in good yield (Scheme 52). The reported stereochemical outcome of this cycloaddition was the basis for designing the second generation approach.

Scheme 52



This advanced model study follows the logic of the previously discussed approach with a synthon that allows for the incorporation of the nitrogen side chain, ultimately to be utilized for closure of the D-ring in morphinan **167**. As seen in the retrosynthesis (Figure 5), *cis*-dienediol **170** would be converted to trienes such as **169** which contain a potential leaving group (X= Cl, Br, OTs, etc.). The key intramolecular Diels-Alder reaction via an

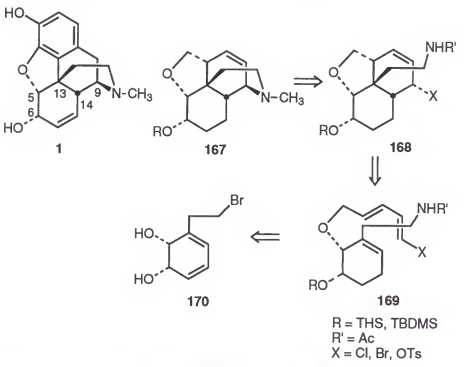


Figure 5. Retrosynthetic plan for 2nd generation IMDA study

endo transition state would lead to tricyclic adduct **168**. Finally, deprotection of the nucleophilic nitrogen and intramolecular S_N2 cyclization would afford tetracycle **167**, a morphinan containing the correct stereocenters found in natural (-)-morphine.

The goal of this dissertation was to further investigate the intramolecular Diels-Alder cyclization, prove the stereochemical outcome, and apply it toward the construction of the nonaromatic portion of (-)-morphine. It was necessary to obtain a firm understanding of the stereochemical outcome of the Diels-Alder cyclization in order to design triene systems which would allow for the subsequent D-ring closure. In addition, suitable protecting groups for both the nitrogen at the C_{16} position and the hydroxyl group at C_6 which could survive the conditions of the Diels-Alder reaction, and, in the case of the

nitrogen, one which could be readily removed or converted to an N-methyl functionality were established.

The discussion section is divided into 3 major sections as follows: 1. Advanced Intramolecular Diels-Alder Study, 2. Terminally Functionalized Diene Tethers, and 3. IMDA Study - Ether and Ester Tethered Systems. Each section addresses a specific task and will conclude with a summary. Finally, some speculation on future investigations will be described in the dissertation conclusions (Chapter 4).

Advanced Intramolecular Diels-Alder Study

On the assumption that the first generation Diels-Alder reaction proceeded via the *endo* transition state, the advanced model study was designed (Figure 6). To begin this investigation, we set out to synthesize target tricycle **171** by analogous Diels-Alder methodology. This approach would parallel that of the previous first generation investigation strategy, differing only in the substitution at the incipient C_{13} of morphine (methyl converted to 2-acetamidoethyl). We initially chose to retain the methyl group at the incipient C_9 of morphine, and intended to change the terminal group after we obtained more information on the stereochemical outcome of the intramolecular Diels-Alder cycloaddition.

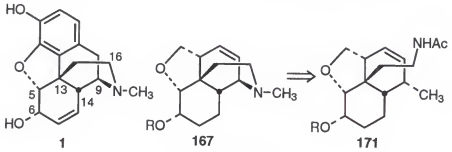


Figure 6. Retrosynthetic plan for initial model system

Synthetic Approach

To begin the synthesis an appropriate arene starting material had to be selected. There were three major requirements for the starting arene: 1) it had to be readily available, 2) it had to be a suitable substrate for the microbial dihydroxylation, and 3) it had to contain

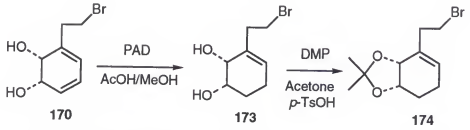
a functionalized side chain which could be chemically manipulated after the enzymatic step. Previously, the Hudlicky group reported the whole cell biooxidation of commercially available (2-bromoethyl)benzene **172** (Scheme 53) with the genetically engineered *E. coli* strain JM109(pDTG601) which readily afforded *cis*-dienediol **170** stereospecifically in good yield, approximately 10 g/L.[86] This synthon would ultimately make up the C-ring of morphine where the correct stereochemistry of C_5 and C_6 were established with excellent enatioselectivity (ee <99%) in the enzymatic step, and the primary halide provided the desired functional handle for subsequent introduction of the nitrogen atom.

Scheme 53

172 **170**

The installation of the nitrogen atom became the next objective. Since *cis*-dienediols are known to readily form phenols by dehydration,[87] it was necessary to immediately reduce the least substituted double bond via diimide reduction with potassium azodicarboxylate ($KO_2CN{=}NCO_2K$) to afford diol **173**. Since diol **173** also readily formed a furan even under mild basic conditions,[88] protection of the diol as its acetonide **174** was necessary (Scheme 54).

Scheme 54

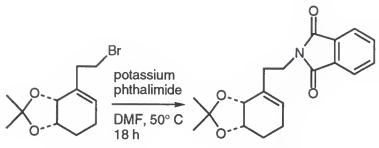


170 **173** **174**

The initial choice for the introduction of the nitrogen onto the side chain was via displacement of the bromide in acetonide **174** with potassium phthalimide to afford

phthalimide **175** (Scheme 55). This S_N2 displacement was readily achieved in either refluxing ethanol or in DMF (50° C, 18 h), however when DMF was employed an excellent yield (95%) was repeatedly attained. The reason for selecting the phthalimde was that it was both readily reduced to the primary amine and very stable at elevated temperatures, a necessary requirement for investigating the thermal Diels-Alder reaction.

Scheme 55

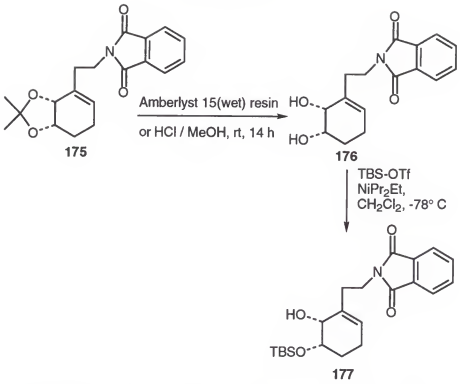


174 **175**

The next objective was to liberate the diol and selectively protect the homoallylic hydroxyl to provide the allylic alcohol necessary for the introduction of ether tethered dienes (Scheme 56). Acetonide **175** was subjected to standard cleavage conditions (Amberlyst 15 wet ion exchange resin in MeOH or HCl/H_2O in MeOH) to afford diol **176** The diol **176** was then protected at the more accessible homoallylic hydroxyl with TBDMS-OTf ($(iPr)_2NEt$, CH_2Cl_2, -78° C) to afford silyl ether **177** in good yield (87%). The protection could also be performed with TBDMS-Cl, however the reaction with the triflate was achieved in superior yield and at a dramatically accelerated rate.

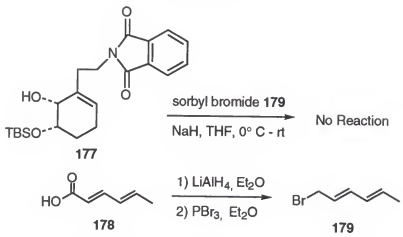
At this point, we began to investigate methods for introducing diene moieties at the allylic hydroxyl position (C_5). In order to closely follow the model previously described, sorbyl bromide **179**, easily prepared in two steps from sorbic acid(2,4-hexadienoic acid),[89]

Scheme 56



was selected as the first model diene tether (Scheme 57). However, after repeating the alkylation conditions (NaH, THF, 0° C) only starting material was recovered and no formation of an ether product was observed.

Scheme 57



Inspection of phthalimide **177** reveals that the allylic hydroxyl is a very sterically hindered site. With the initial lack of success, a series of electrophiles and conditions were

studied to better understand the reactivity at the allylic position (Table 2). In all cases, no alkylation product was observed. Most interesting to note is that even the smallest, most reactive electrophile, methyl triflate, did not react at the allylic hydroxyl site.

Electrophile	Conditions	Result
allyl bromide	NaH, THF, rt	rec. starting material
"	K_2CO_3, acetone, rt	"
"	K_2CO_3, neat, 60° C	"
"	K_2CO_3, neat, 185° C	decomposition
methyl iodide	K_2CO_3, acetone, rt	rec. starting material
methyl triflate	NEt_3, CH_2Cl_2, -78° C	"

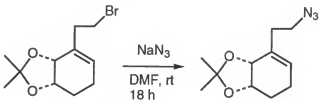
Table 2. Alkylations attempted on phthalimide 177

Another possibility for the lack of reactivity may be attributed to the migration of the silyl group under the conditions of the reaction. The silyl migration was in fact observed when the HPLC was used to monitor the reaction of methyl iodide with the phthalimide **177**. An aliquot of the starting material showed a ratio of 100:1 in favor of the homoallylic protected phthalimide **177**, but after refluxing the reaction overnight, a second HPLC run of the reaction mixture showed that the ratio had changed to 4:1. To prove that the new peak was attributed to the product of silyl migration and not a reaction product, a third HPLC run was taken of the starting material after stirring for 5 minutes in the presence of potassium carbonate and acetone which showed a ratio change from 100:1 to 40:1. So, not only did sterics play an important role in rendering the allylic hydroxyl unreactive, contributing difficulties with silyl migration rendered the phthalimide substrate unsuitable for the model study. For these reasons, we looked to change both the nitrogen moiety on the ethyl side chain as well as the silyl protecting group.

Because of the inability to alkylate phthalimide **177**, we sought to incorporate the nitrogen functionality with a sterically less demanding group. The nitrogen atom was thus introduced in the form of an azide, which could also be readily reduced at a later time to the

desired primary amine (Scheme 58). Installation of the nitrogen by nucleophilic displacement of the bromide in acetonide **174** with sodium azide in DMF was achieved affording the azide **180**. Although the displacement also worked in ethanol and DMSO, the isolated yield was higher when DMF was used as the solvent.

Scheme 58

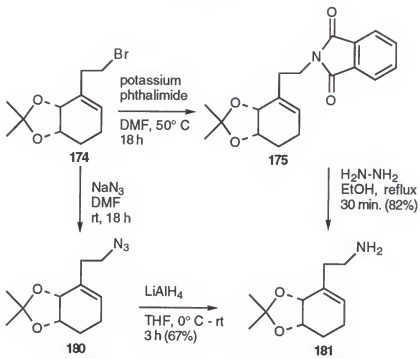


Concurrent with the search for methods of introducing the nitrogen onto the ethyl side chain, we investigated techniques for converting the substrate to the ultimately desired N-methyl compound. The goal of this study was to establish a viable route for installation of the N-methyl functional group, and at a later time, for incorporating this into the total synthesis.

The N-methylation strategy could start from either phthalimide **175** or azide **180**, both of which were ultimately derived from (2-bromoethyl)benzene diol **170** (Scheme 59). Both the phthalimide **175** and the azide **180** could be readily reduced to the corresponding primary amine **181**, in the former via traditional Gabriel conditions or in the latter by $LiAlH_4$ reduction. The yield of both of these routes was comparable (82% vs. 67%), however, experimentally the phthalimide **175** reduction was faster and much easier to work up and purify (filtration, followed by washing with CH_2Cl_2, and isolation by extraction with 10% citric acid).

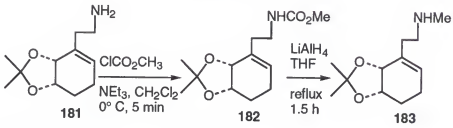
We turned toward methods for incorporating the N-methyl group. The amine **181** was thus reacted with methylchloroformate to afford carbamate **182** readily isolated by column chromatography in good yield (86%). Reduction of carbamate **182** with $LiAlH_4$

Scheme 59



afforded the N-methyl acetonide **183** (Scheme 60). Thus, in 2 steps we achieved the desired transformation and formalized a strategy for N-methylation which could later be incorporated into the synthesis.

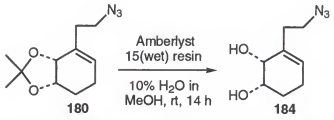
Scheme 60



After we had established an efficient route to the installation of the N-methyl functional group, we returned to synthesizing model trienes for the intramolecular Diels-Alder investigation. In order to functionalize azide **180** to the desired ether tethered triene, we first needed access to the allylic hydroxyl group. Cleavage of the acetonide was accomplished by stirring in 10% H_2O/MeOH over Amberlyst 15(wet) ion exchange resin to afford azidodiol **184** (Scheme 61). It was necessary to add 10% water to the reaction

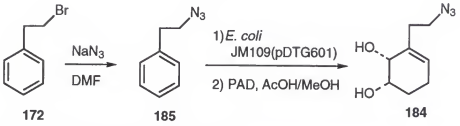
mixture in order to drive the deprotection to completion. The azidodiol **184** contained the necessary functionality for construction of the desired ether diene tethers.

Scheme 61



Alternatively, azidodiol **184** could be obtained by direct microbial dihydroxylation of (2-azidoethyl)benzene **185**, generated in one step from commercially available (2-bromoethyl)benzene **172** and isolated by distillation at reduced pressure (bp = 30° C, 0.01 mm Hg). When (2-azidoethyl)benzene **185** was subjected to enzymatic biooxidation with *E. coli* JM109(pDTG601), the desired *cis*-dienediol could be isolated in modest yield, 6 g/L, with 70% conversion.[90] Reduction of the least substituted double bond with diimide was performed on the crude dienediol to afford the reduced diol **184** and thus shortened the synthesis by two steps. Furthermore, problems associated with intramolecular closure to furans as described previously were alleviated (Scheme 62).

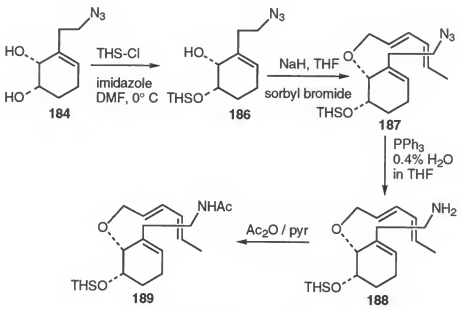
Scheme 62



The desired tethers for the intramolecular Diels-Alder study were to be constructed by etherification of the allylic hydroxyl group (C_5 of morphine), thus it was necessary to find a protecting group for the homoallylic hydroxyl group (C_6 of morphine). In the first generation model study, the thexyldimethylsilyl ether was stable under the thermal cyclization conditions, so likewise, diol **184** was protected almost exclusively at the less hindered homoallylic cite with thexyldimethylsilyl chloride to afford silyl ether **186**

(Scheme 63). Etherification of the sodium alkoxide of azidoalcohol **186** with sorbyl bromide **179**, afforded triene **187**. Since it is well know that azides can rearrange and undergo 1,3-dipolar cycloadditions at high temperatures, it was necessary to synthesize a more suitable protected nitrogen functionality. The azide **187** was thus reduced to the corresponding primary amine **188** with triphenylphosphine and subsequently protected as an acetamide with acetic anhydride / pyridine to afford the desired triene **189**.

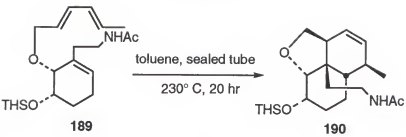
Scheme 63



The first intramolecular Diels-Alder cyclization of triene **189** was performed under standard thermal conditions following the previously reported approach as closely as possible (toluene, sealed tube, 230° C, 20 h). We performed the reaction in a preheated sand bath to insure even heating of the sealed reaction tube. Cycloadduct **190** was isolated as a single stereoisomer in 62% yield (Scheme 64).

We next had to address the stereochemical outcome of the intramolecular Diels-Alder cyclization. Assignment of the stereochemistry by standard proton NMR experiments was ambiguous, so we subjected tricycle **190** to a 2D TOCSY NMR experiment in hopes of obtaining more information about both the connectivity and coupling of the cycloadduct.

Scheme 64



189 **190**

The assignment of the protons was made after careful analysis of the TOCSY NMR experiment. In order to assist in the explanation of the assignments, we numbered the carbon atoms in tricycle **190** with the same numbers they would receive in natural (-)-morphine (Figure 7). It is easiest to start the assignment downfield with the vinyl protons connected to C_{10} and C_{11} at 5.64 and 5.57 ppm respectively. The proton at 5.64 ppm was assigned to C_{10} because of two weak cross peaks showing a coupling back into the methylene envelope, while the proton at 5.57 ppm was assigned to C_{11}, which showed only a coupling with C_{10}. The next proton, a broad singlet at 5.44 ppm, was assigned as the exchangeable proton attached to the nitrogen on the acetamide protecting group.

The next region of interest was the area between 4.10 and 3.10 ppm, which contained all 6 of the protons next to the heteroatoms in the compound. Inspection of the splitting patterns allowed us to determine the protons at C_4 shifted to 4.10 and 3.54 ppm respectively. The shift suggested that the protons were adjacent to an oxygen atom, and both of these signals were split into a doublet of doublets, which suggested one geminal and one vicinal coupling for each proton. The marked shift difference between the two C_4 protons, ~ 0.6 ppm, is explained easily after inspection of a model of the cycloadduct. One of the C_4 protons lies in the concave face of this rigid molecule and is significantly deshielded with respect to the other. The next assignment at 3.95 ppm was given to theproton at C_6, which was deduced by observation of both the broadened splitting of the signal and the cross peaks with not only the C_5 proton but also two other weak couplings with the methylene envelope. That left the doublet at 3.71 ppm assigned to the C_5 proton,

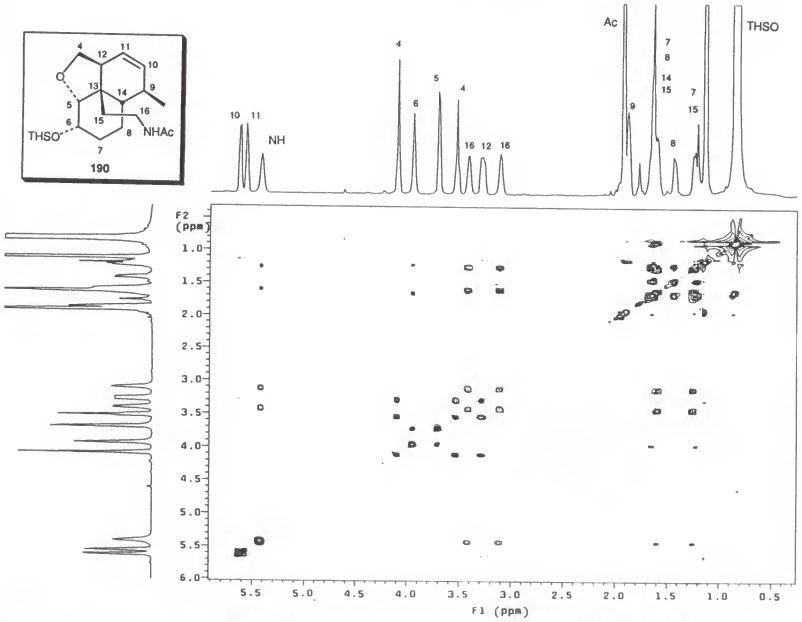


Figure 7. TOCSY NMR - Assignment of cycloadduct 190

showing only the coupling with C_6. Next, the protons at C_{16}, which were adjacent to a nitrogen, were assigned to the multiplets at 3.42 and 3.12 ppm. These two protons showed a strong coupling with each other as well as a cross peak showing coupling into the methylene region.

Perhaps the most interesting conclusion from the TOCSY experiment was the assignment made for the allylic bridgehead proton C_{12} when compared to its allylic counterpart on C_9 at 1.90 ppm. Inspection of the coupling patterns allowed for theassignment of the allylic bridgehead proton as the multiplet at 3.29 ppm, which showed only coupling with the protons at C_4. The shift seemed markedly downfield for an allylic proton, however the C_{12} was obviously deshielded significantly by the ring suggesting that it may lie in the concave face of the molecule. The allylic proton at C_9 was not affected by these interactions since it was several atoms removed from the ring fusion.

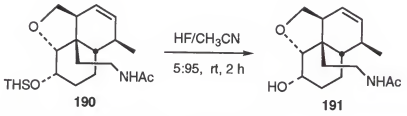
The final region for assignment was the methylene region form 1.70 to 1.00 ppm. According to the integration, the complicated multiplet at 1.64 ppm contained five different protons, one of which belonged to the thexyl protecting group. The other four protons were assigned to C_{15}, C_{14}, C_8, and C_7 by careful inspection of the cross peaks. The second C_8 proton was assigned to the multiplet at 1.44 ppm which showed couplings to the multiplet at 1.64 ppm. The final two methylene protons contained in the multiplet at 1.27 ppm were assigned to C_{15} and C_7. The three protons contained in the doublet at 1.14 ppm were assigned as the protons on the methyl substituent at C_9. To finalize the total assignment, we noted that the singlet at 1.94 ppm was the acetamide methyl protons, and the signals at 0.87, 0.83, 0.12, and 0.08 ppm, integrating for eighteen protons, were attributed to the thexyldimethyl silyl protecting group on the C_6 oxygen.

Structure Proof

The 2D NMR analysis provided significant information on the connectivity of the cycloadduct, but we still did not know the absolute stereochemistry of tricycle **190**. Thus, we felt confident that cleavage of the silyl protecting group in tricycle **190** would afford

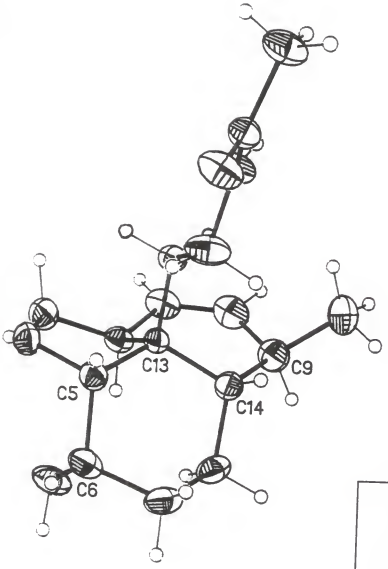
alcohol **191** from which a single crystal could be grown for X-ray crystallographic analysis (Scheme 65). The cleavage was successful when tricycle **190** was stirred at room temperature in HF/CH_3CN to give tricyclic alcohol **191**. A single crystal of the free alcohol **191** was successfully grown when a sample of the alcohol was sealed in an NMR tube and the chloroform was allowed to slowly evaporate over five to six weeks.

Scheme 65



190 **191**

X-ray crystallographic analysis of the free alcohol confirmed the stereochemistry of cycloadduct **191** (Figure 8) and revealed that the [4+2] cycloaddition proceeded via an *exo* transition state, which was the opposite stereochemistry to that reported in the first generation model study in 1992. It is noteworthy that cycloadduct **191** contains all 5 chiral centers of natural (-)- morphine in the correct absolute configuration, apparent in the X-Ray structure.



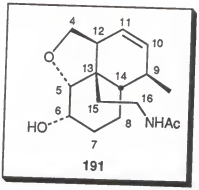


Figure 8. X-Ray of tricyclic alcohol 191

Inspection of the two possible transition states of the intramolecular Diels-Alder reaction along with the stereochemical proof of the isolated product demonstrated the importance of the steric effects in the cycloaddition. Figure 9 shows that in the *endo* transition state **193**, where the diene tether is forced underneath the cyclohexene ring, the diene has an unfavorable interaction with not only the hydrogens in the cyclohexene ring but more importantly with the large dimethylthexysilyl protecting group. In the *exo* transition state **192** however, the diene positions itself outside of the cyclohexene ring and has much less interaction with the silyl protecting group and the ring hydrogens. Thus, the steric influences prevailed and only the *exo* adduct **190** was isolated.

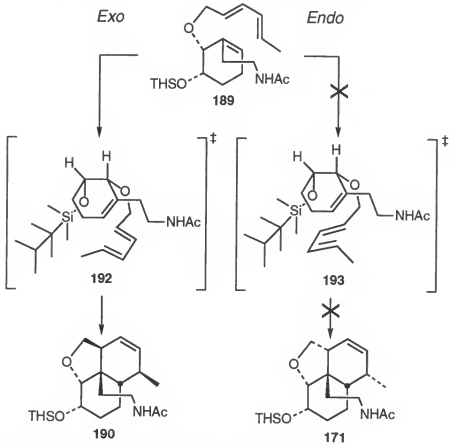


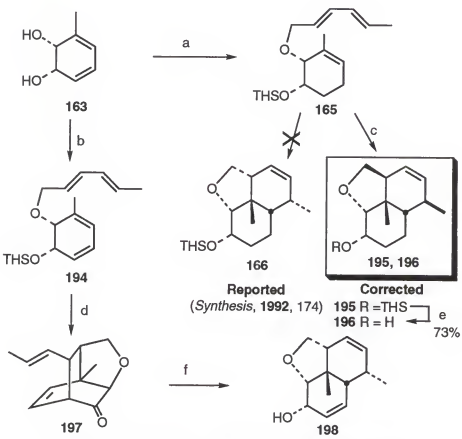
Figure 9. *Exo* versus *Endo* Transition State

Structure Correction of the Previously Reported Diels-Alder Adduct

On the basis of this new observation, the first generation approach was reinvestigated to determine the absolute stereochemistry of the previously reported *endo*

adduct **166** (Scheme 66). In the first generation model study, a Diels-Alder / Cope rearrangement sequence or a Diels-Alder cyclization was used to obtain the reported tricyclic adducts **198** and **166** respectively. The stereochemical outcome of the first route is determined in two separate stereospecific reactions. In the initial Diels-Alder cycloaddition, the cyclohexadiene reacts with the internal olefin of the tether acting as the

Scheme 66



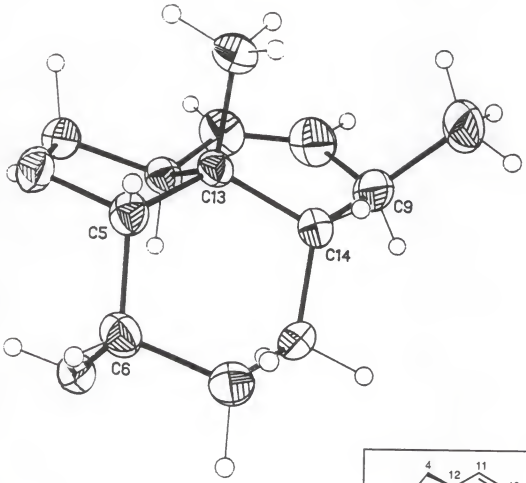
THS = dimethylthexylsilyl = dimethyl(1,1,2-trimethylpropyl)silyl

a: i. potassium azodicarboxylate (PAD), AcOH, MeOH
ii. THS-Cl, imidazole, DMF, iii. NaH, sorbyl bromide, THF
b: i. THS-Cl, imidazole, DMF, ii. NaH, sorbyl bromide, THF
c: toluene, sealed tube, 210° C, 24 h
d: i. CCl_4, reflux, 7 h, ii. $Bu_4NF{\bullet}3H_2O$, THF, rt, 24 h
iii. PCC, CH_2Cl_2, rt, 24 h
e: HF/CH_3CN (5:95), 12 h
f: i. xylenes, sealed tube, 250° C
ii. $NaBH_4$, $CeCl_3{\bullet}7H_2O$, MeOH, rt, 15 min.

dienophile. The Cope rearrangement of the caged structure **197** can only proceed through a single pathway leading to the tricyclic adduct **198** with shown stereochemistry.

However, in the second route, the intramolecular Diels-Alder reaction can proceed via an *endo* or *exo* transition state. Unfortunately the two adducts were not converted to common intermediates for unambiguous comparison. This could have been easily achieved with simple deprotection and hydrogenation to the fully saturated tricycles. Therefore the synthesis was repeated, and indeed the *exo* adduct **195** was isolated. Analogous deprotection of silyl ether **195** to the free alcohol **196** and X-ray crystallographic analysis confirmed the structure as *exo* cycloadduct **196** (Figure 10). Therefore, this observation has been submitted as a structure correction for the previous Diels-Alder model study.[91]

Important conclusions can be made from this second generation model study. The stereochemical outcome of the Diels-Alder cyclization, between a neutral diene and a trisubstituted neutral dienophile, was controlled by the steric interactions in the transition state. The exclusively isolated *exo* cycloadducts **191** and **196** in both thermal reactions, as proven by X-ray crystallography, demonstrated the importance of steric control in the intramolecular Diels-Alder reaction, which clearly took precedent over any electronic considerations. Most importantly, by understanding the stereochemical outcome of the cycloaddition, we now had a precedent which could be applied in the design of more advanced triene systems and ultimately toward a more advanced morphinan.



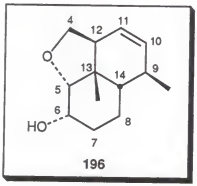


Figure 10. X-Ray structure of tricyclic alcohol 196 - structure correction

Terminally Functionalized Diene Tethers

With a better understanding of the stereochemical outcome of the intramolecular Diels-Alder reaction on the ether tethered system, we turned toward designing precursors which would allow for the alkylative ring closure of the D-ring following the [4+2] cycloaddition. We planned to take advantage of the stereochemical outcome of the intramolecular Diels-Alder and envisioned two convergent approaches, both of which would utilize chiral *cis*-(2-ethylbromo) dienediol **170** as the starting material (Figure 11).

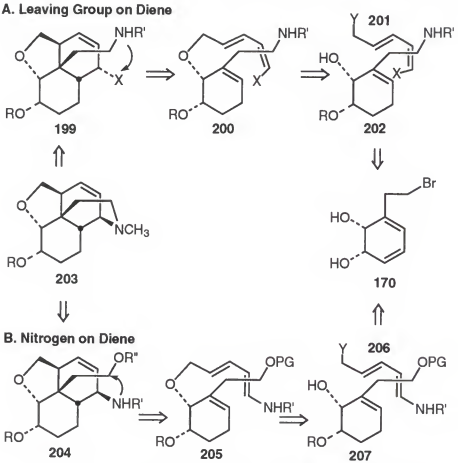


Figure 11. Retrosynthetic plan for final ring closure

The first pathway A would install a terminal leaving group on the diene tether. The important element of this pathway is that the *E,Z*-diene would be constructed. Dienediol **170**, after conversion to the protected alcohol **202**, would be alkylated with the

independently synthesized *E,Z*-halodiene **201**. The anticipated *exo* cycloaddition of ether **200** would afford tricycle **199**. The stereochemistry at the incipient C_9 would be opposite to that observed in the cyclization of triene **189** to *exo* cycloadduct **190**, which utilized an ether tethered *E,E*-diene. After unmasking the protected nitrogen, an intramolecular S_N2 closure would afford morphinan **203** with the correct stereochemistry of natural (-)-morphine.

Pathway B simply switches the position of the nitrogen and leaving group and again relies on the anticipated *exo* cycloaddition. By this route, the bromide of dienediol **170** would initially be replaced with a protected oxygen moiety. Alkylation of alcohol **207** with a terminal nitrogen diene **206** would afford the Diels-Alder precursor triene **205**. The anticipated *exo* cyclization would provide tricycle **204**. After conversion of the protected oxygen to a leaving group and unmasking the protected nitrogen, closure via an intramolecular S_N2 reaction analogous to that in Pathway A would provide the identical morphinan **203**.

We thus investigated these two pathways in hopes of synthesizing morphinan **203**. Since both of the pathways proceeded from the same starting *cis*-dienediol **170**, they were pursued in parallel.

Terminal Chlorodiene Tethers *E,Z* and *E,E*-Dienes

Assuming that the intramolecular cyclization would continue to be sterically controlled and proceed via the *exo* transition state, a model system was designed which would incorporate a leaving group at the terminal end of the diene tether. As depicted in the retrosynthesis (Figure 12), either an *E,Z* or *E,E*-halodiene would provide the leaving group at the incipient C_9 of morphine. Cyclization of the *E,Z*-diene **200** via the *exo* transition state would provide tricycle **208**, which would be set up directly for the desired intramolecular S_N2 cyclization after deprotection of the nitrogen. In the case of *E,E*-diene **209**, the adduct analogous to the previously discussed examples would provide the halide

on the β–face of the molecule and would require an inversion (Finkelstein reaction) prior to the final ring closure.

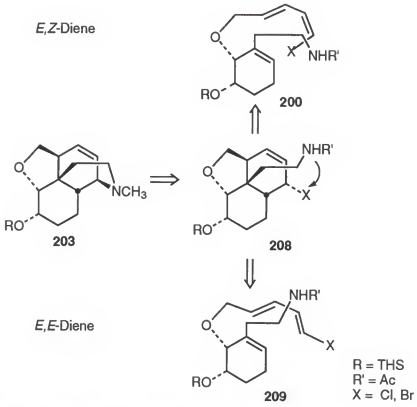
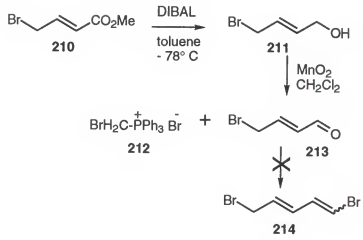


Figure 12. Retrosynthesis of *E,Z* and *E,E*-dienes

The initial idea was to synthesize known aldehyde[92] **213** and subject it to a Wittig reaction with bromomethyl(triphenyl)phosphonium bromide[93] **212** (Scheme 67). In this

Scheme 67

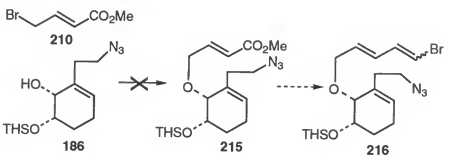


flexible approach, two separate routes were investigated in parallel. The ester **210** could either be initially connected to the model azidoalcohol **186** and then subjected to reduction, oxidation and the Wittig reaction or diene **210** could be constructed first and then used as the electrophile in construction of the ether tethered triene.

The known aldehyde **213** was synthesized according to the literature procedure in crude yield of 78% (lit. value 88%). While the authors had no problem performing a Wittig reaction of aldehyde **213** with (methoxycarbonylmethylene)triphenylphosphorane (70.5%), we had no success in the Wittig reaction with bromomethyl(triphenyl)-phosphonium bromide **212** in neither *n*BuLi / toluene - 78° C nor potassium *t*-butoxide / THF - 78° C both of which resulted in a complex mixture of products, and no isolation of the desired diene.

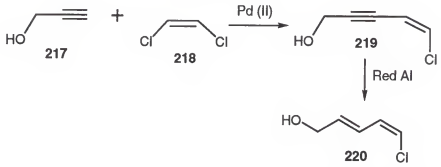
In parallel with the independent diene synthesis, a stepwise route was investigated whereby ester **210** would be alkylated directly to azidoalcohol **186** and then subjected to the sequence discussed above to hopefully afford the desired tethered triene **216** (Scheme 68). Unfortunately, ether **215** could not be obtained through standard Williamson conditions which were successful in the previous model. Attempts at the etherification of azidoalcohol **186** with aldehyde **213** and alcohol **211** also failed to afford any O-alkylation products. Only the recovered starting material and the decomposition of the electrophiles **210**, **211**, and **213** resulted. Therefore, we were unable to investigate the Wittig reaction and needed to search for another route for preparing the terminal halodienes.

Scheme 68



A literature search provided us with a recent report by Linstrummelle and coworkers which described the use of palladium to couple various propargyl alcohols with dihaloethylene to provide enynes (Scheme 69).[94] This method would provide the *E,Z*-diene when propargyl alcohol **217** is coupled with *cis*-dichloroethylene **218** followed by

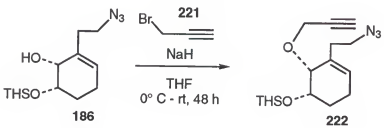
Scheme 69



reduction of the intermediate enyne **219** with Red-Al to afford diene **220**. By simply utilizing *trans*-dichloroethylene, the *E,E*-diene system could be obtained by the identical procedure. Conversion of the alcohol to a leaving group would provide a suitable diene for alkylation to the model mono protected azidoalcohol **186**.

Initial investigation of the palladium coupling strategy proceeded from azidoalcohol **186** with the intention of constructing the diene tether in a stepwise fashion. Since we had previously established that the ether synthesis proceeded by treating azidoalcohol **186** with sodium hydride and then introducing the alkyl bromide, the sodium alkoxide of azidoalcohol **186** was reacted with propargyl bromide **221** to afford azidoether **222** in 72% yield (Scheme 70). With the intention of isolating both the *E* and *Z* coupled enynes,

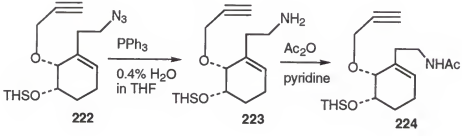
Scheme 70



alkyne **222** was then subjected to palladium coupling ($PdCl_2(PPh_3)_2$, CuI, $EtN(iPr)_2$, benzene) with a *cis,trans* mixture of 1,2-dibromoethylene, however no desired coupled products were observed.

Since it would require one less inversion sequence in the final ring closure step, we instead set out to construct the *E,Z*-diene tether exclusively. Additionally, because we wanted to pursue thermal Diels-Alder cycloadditions, conversion of the azide to an acetamide was necessary. Thus, azide **222** was converted in a two step reaction to give acetamide **224** in 66% overall yield (Scheme 71). Acetamide **224** was then subjected to palladium coupling conditions with *cis*-dichloroethylene under a variety of conditions.

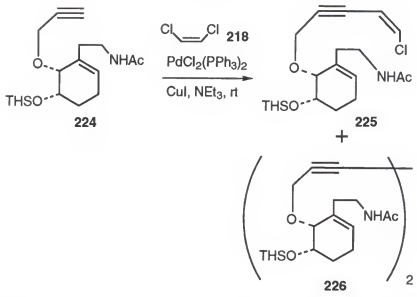
Scheme 71



While conditions were found which afforded the desired *Z*-enyne **225**, the major compound in each case was the product of dimerization of the starting alkyne to afford dimer **226** (Scheme 72). Because of the poor yield (19%) of this stepwise coupling, combined with such a large loss of an advanced starting material, our efforts were redirected toward a convergent approach.

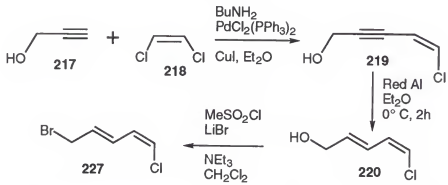
After construction of the known diene **220** and conversion to the bromide **227**, we planned to alkylate azidoalcohol **186** with the bromodiene **227**. The hope was to achieve a higher yielding synthesis of triene **228** via a know diene synthesis combined with the

Scheme 72



existing methods for the ether construction. Following known literature procedures the coupling of propargyl alcohol **217** with *cis*-dichloroethylene **218** afforded enyne **219** in 70% yield (Scheme 73).[95] Although the authors purified the enyne **219** by distillation, we

Scheme 73

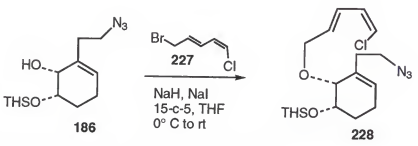


achieved a higher yield by purifying the crude product by column chromatography through a plug of silica gel (1:1 pentane/diethyl ether). Exclusive *trans* reduction of the internal alkyne was achieved with Red-Al to afford known chlorodieneol **220**. After quick purification through a plug of silica gel, the alcohol was converted in a one pot sequence to the corresponding bromide **227**, via a mesylate intermediate, which was purified by

column chromatography with the identical eluent system (1:1 pentane/diethyl ether) and isolated in 71% yield.

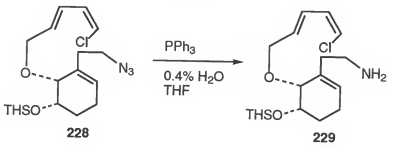
Synthesis of the ether was the next concern, so we returned to know methods for the O-alkylation. The sodium alkoxide of azidoalcohol **186** was successfully reacted with bromodiene **227** to afford the desired triene **228** in 56% isolated yield (Scheme 74). The yield was found to be heavily influenced by the concentration of the reaction mixture and was optimized by performing the reaction at a concentration of 50 mg/mL along with NaI and 15-c-5 crown ether as catalysts. This method afforded an adequate amount of the triene **228** without the sacrifice of valuable advanced starting materials.

Scheme 74



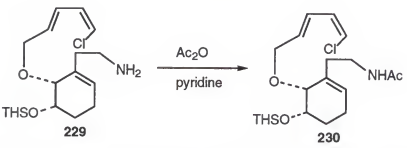
We next had to convert the azide to a thermally stable protected nitrogen compound in order to continue toward the key intramolecular Diels-Alder cyclization. The azidotriene **228** was reduced to amine **229** with triphenyl phosphine in a modest yield of 46% (Scheme 75). Purification by column chromatography using a buffered eluent (ethyl acetate saturated with ammonium hydroxide) not only eluted the desired amine **229** but

Scheme 75



also washed out silica gel and ammonium salts. The amine could be filtered away by dissolving into hexanes, but inherent loss of product could not be avoided. The amine **229** was subsequently protected as an acetamide with acetic anhydride in pyridine to give the desired Diels-Alder triene **230** (Scheme 76).

Scheme 76

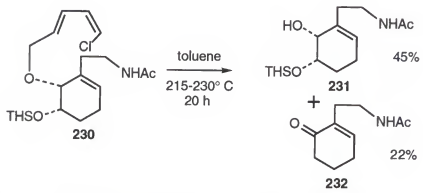


With the synthesis of the triene system established, we turned to the investigation of the intramolecular Diels-Alder reaction. Initially to compare the reactivity with the previously discussed triene **189**, we subjected triene **230** to identical thermal Diels-Alder conditions. After heating triene **230** in toluene in a sealed tube at ~ 230° C for 20 hours, the starting material was consumed and three major products were observed by TLC. Proton NMR spectra of the crude product mixture showed the presence of at least 2 olefinic protons and also indicated that the silyl protecting group was still present in the mixture.

Since the crude NMR appeared promising, we purified the crude mixture by column chromatography, and the three main products were isolated. The total amount of starting material in the reaction was 17.6 mg, from which was isolated a total of 11.6 mg of products. The first product isolated, the one with the highest R_f (0.79 in 100% EtOAc) was identified as a silyl ether residue. Proton NMR spectra of this fraction, comprised of 4 mg of a yellowish oil, clearly showed the presence of protons near a silicon atom, but absolute identification of the structure could not determined. The second product isolated was identical to acetamide **231** (6 mg, 45%), whose synthesis via a different route is described later in this chapter, resulting from elimination of the diene side chain. The final product

isolated was enone **232** (1.6 mg, 22%), determined only after careful inspection of the ^{1}H and ^{13}C NMR spectra as well as the high resolution mass spectrum (Scheme 77).

Scheme 77



The ^{1}H NMR spectrum of enone **232** clearly showed one olefin signal 5.87 ppm as well as the amide proton at 5.46 ppm. The third characteristic signal was the acetamide methyl singlet at 1.97 ppm. Only 10 more protons remained, the two at 3.46 ppm were assigned to the protons alpha to the acetamide. Finally the multiplet at 2.38 ppm, integrating for 6 protons, and a pentet at 1.99 ppm were assigned to the remaining methylene signals.

The ^{13}C NMR spectrum was not conclusive because of the small amount of isolated product, but some information was obtained. Inspection of the spectrum showed the presence of a signal at 127.0 ppm, attributed to the vinyl CH carbon, and 6 more signals at 38.0, 37.2, 36.8, 29.7, 29.4 and 22.6 respectively. These 6 signals were assigned to the 5 methylene carbons and the CH_3 of the acetamide protecting group. Unfortunately, signals for the 3 quaternary carbons in enone **232** were not observed even after 8.3 hours of acquisition.

It was not until the mass spectrum was obtained that the structure of enone **232** was determined and confirmed the results of the NMR experiments. Three important signals were identified. The first at 363 mmu which was attributed to the M+H of dimerized enone **232**, a common observation in the mass spectra of conjugated enones. The molecular ion M+H was observed at 182 mmu, in accordance with the mass of the

enone **232**. The third conclusive peak at 123 mmu corresponded to the loss of the acetamide group from the ethyl side chain. Thus, inspection of these three data allowed us to assign the structure of the enone **232**.

The unfortunate conclusion made from this Diels-Alder cyclization attempt was that cleavage of the starting triene **230** occurred more readily than the desired cycloaddition. Positive identification of alcohol **231** showed that the terminal chlorodiene tether could not withstand the thermal conditions required for the cycloaddition. Isolation of enone **232**, which can only be attributed to cleavage of the silyl protecting group followed by dehydration, further suggests that the thexyl protecting group is possibly removed by chlorine generated after the diene is cleaved from the starting material. To overcome the cleavage problems in this system would require either alteration of the silyl protecting group or stabilization of the chlorodiene.

Terminal Nitrogen Dienes

A second logical approach for designing the next triene system, assuming that the *exo* cycloadduct would again prevail in the Diels-Alder reaction, was to reverse the position of the nucleophilic nitrogen and the leaving group. As seen in the retrosynthesis (Figure 13), closure to tetracycle **203** could also be achieved when the nitrogen is installed at the incipient C_9 of morphine **1** and the leaving group at C_{16}. Tricycle **233**, the predicted *exo* adduct, would be obtained by the Diels-Alder reaction of triene **234** which is ultimately derived again from the chiral dienediol **170** and an appropriate dienamine or dienamide **235**.

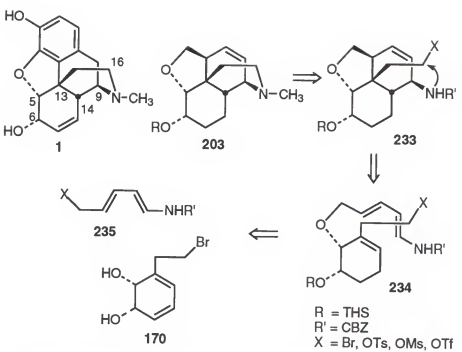
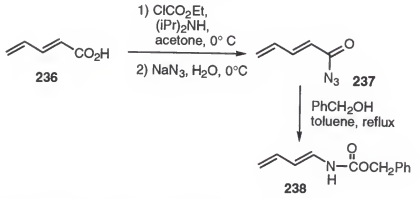


Figure 13. Retrosynthetic plan for terminal nitrogen diene

With this retrosynthetic plan, we searched the literature for methods of preparing dieneamides similar to **235**. A report by Overman and coworkers showed that *trans*-2,4-pentadienoic acid **236** could be converted to protected dieneamide **238** via the acyl azide **237** in a two step process (Scheme 78).[96] The most notable step in the process was the Curtius rearrangement of acyl azide **237** to the corresponding dieneamide **238** in the presence of benzyl alcohol. Dieneamide **238**, or derivatives thereof, were of particular

Scheme 78



interest because the CBZ group could potentially be reduced to the N-methylamine, which was desired in the final target molecule **203**.

Assuming we could apply Overman's method for the rearrangement of acylazide **240**, generated after Diels-Alder cyclization of the corresponding ester **241**, we proposed a retrosynthesis (Figure 14). The key step in the retrosynthesis was the Curtius rearrangement of acyl azide **240** to afford the CBZ protected amide **239**. Our intention was to successfully cyclize triene **241** and then subject the cycloadduct to hydrolysis and subsequent acyl azide formation to give **240**. Ultimately triene **241** would be derived from alkylation of *cis*-dienediol **170** with the dienoic ester **242**.

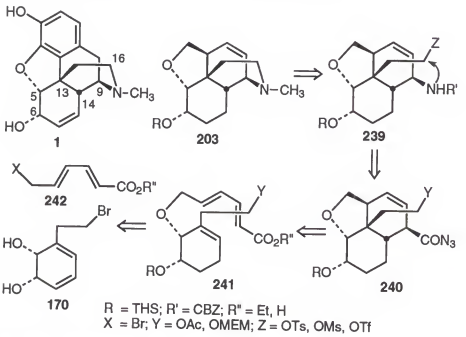


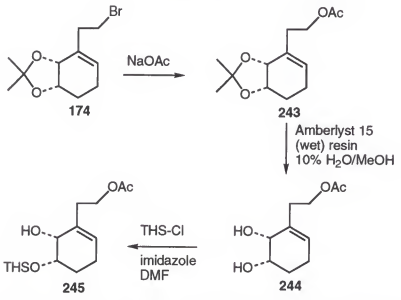
Figure 14. Retrosynthesis via Overman's acylazide rearrangement

Unlike the two previously described model trienes, triene **241** would contain a terminal ester group which would significantly change the electronics of the diene. The ester would render the diene a Michael type acceptor making the diene more electrophilic and thus enhance the reactivity of the cycloaddition. With this idea, we sought methods for synthesizing diene **242** where X = Br and R" = Et.

In order to pursue the Curtius rearrangement, it was necessary to install a protecting group on the ethyl side chain which could later be unmasked and converted into a leaving group. Initially we chose to exchange the bromine with acetate, which could be cleaved

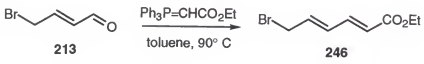
under basic conditions after the appropriate diene was in place. The recently reported acetate **243** was easily synthesized from bromoacetonide **174**.[90] Subsequent cleavage to diol **244** was achieved by stirring acetonide **243** in a methanolic solution of Amberlyst 15 (wet) ion exchange resin. (Scheme 79). Diol **244** was then protected as the monosilyl ether **245**. Based on previous experiments, we felt confident that the thexyl protecting group would survive both the alkylation conditions and eventually the thermal conditions of the pending [4+2] cycloaddition.

Scheme 79



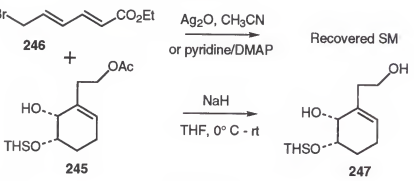
Our next objective was to synthesize the appropriate ester terminal diene. From the previously discussed terminal halodiene efforts, we synthesized the known ethyl 6-bromosorbate **246** via a Wittig reaction of aldehyde **213** with (ethoxycarbonylmethylene)triphenylphosphorane which proceeded in a 39% yield (Scheme 80).

Scheme 80



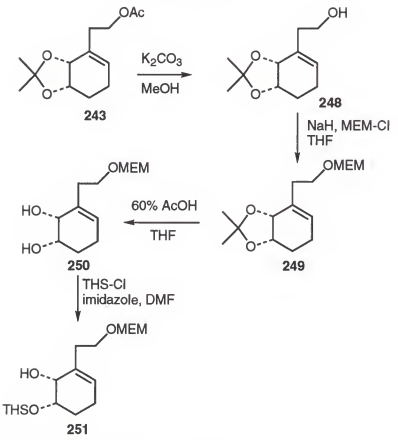
Knowing that acetate **245** would be prone to cleavage under basic conditions, we first attempted the alkylation in the presence of silver oxide and then in pyridine with catalytic DMAP (Scheme 81). Unfortunately under these conditions, no alkylation products were observe. Instead, the diene **246** was consumed and could not be recovered from the reaction mixture. Switching to the basic conditions as a final attempt resulted in the cleavage of the acetate to afford diol **247**. We felt confident that the alkylation conditions could potentially be optimized under basic conditions, so we next sought another protecting group which would be less labile in the presence of base.

Scheme 81



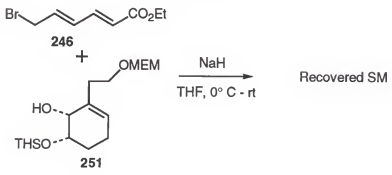
We first considered both the methoxymethyl (MOM) and methoxyethoxymethyl (MEM) protecting groups as suitable replacements for the acetate. Both groups could be readily cleaved with a variety of Lewis acids. However, since the MEM group was less acid sensitive and considering that an acid catalyzed cleavage of the acetonide **249** would be necessary, we chose to initially utilize the MEM protecting group (Scheme 82). Cleavage of the know acetate **243** with a solution of methanolic K_2CO_3 gave alcohol **248**. Methoxyethoxymethyl chloride readily reacted with the sodium alkoxide of alcohol **248** to afford ether **249**. Cleavage of acetonide **249** with 60% acetic acid in THF afforded diol **250** which was subsequently protected at the least hindered homoallylic hydroxyl to give the corresponding thexyldimethylsilyl ether **251**.

Scheme 82



The silyl ether **251** was then subjected to alkylation with the previously prepared bromide **246** (Scheme 83). Introduction of bromide **246** to a solution of the sodium alkoxide of silyl ether **251** unfortunately resulted in only the recovery of starting material. Interestingly, during the course of the reaction the ethyl 6-bromosorbate **246** was consumed. However, a TLC standard of the diene retrieved prior to the alkylation remain-

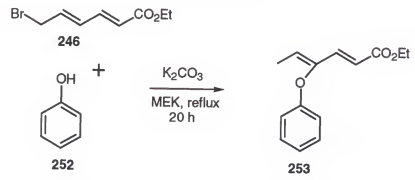
Scheme 83



ed intact. We concluded that ethyl 6-bromosorbate **246** was unstable in the presence of base. Although precautions were taken to prevent moisture from entering the reaction, any minor traces of water under the basic conditions could readily hydrolyze the ethyl ester to the corresponding acid. Furthermore, polymerization of ethyl 6-bromosorbate **246** was possible and offered an explanation for the disappearance of the diene during the reaction.

Inspection of the literature provided critical information from which we based some conclusions regarding the attempts at alkylation of alcohol **251** with ethyl 6-bromosorbate **246**. In 1951 Ungnade and Hopkins reported the alkylation of phenol with ethyl 6-bromosorbate **246** (Scheme 84).[97] When phenol **252** was refluxed with K_2CO_3 and ethyl 6-bromosorbate **246** for 20 hours in methylethyl ketone, only phenoxy ester **253** was isolated in 27% yield. The authors also reported isolation of polymerized material which was non-volatile at 200° C. The formation of the major product was attributed to the formation and rearrangement of an allylic cation, or could alternatively be described as an S_N2' reaction followed by an isomerization to the fully conjugated phenoxy ester **253**. The most important conclusion from this literature example is that the S_N2' reaction was preferred over the S_N2, which showed our desired alkylation was not possible with ethyl 6-bromosorbate **246** as an electrophile.

Scheme 84



When we compared our attempt at etherification with that of Ungnade described above some conclusions were drawn. First, Ungande reported the formation of stable polymeric material which can be attributed to the polymerization of ethyl 6-bromosorbate

246 and provided an explanation for our observation of the disappearance of the sorbate throughout the alkylation attempts. Second, while phenol **252**, an excellent and unhindered oxygen nucleophile, underwent alkylation to give a poor yield of vinyl ether **253**, the less nucleophilic and seriously hindered oxygen in alcohol **251** did not participate in any alkylation, even when first converted to the corresponding alkoxide. Thus, the instability of the electrophile (ethyl 6-bromosorbate **246**) combined with the inaccessibility of the allylic oxygen for alkylation caused us to abandon this route toward advanced model triene systems.

IMDA Study - Ether and Ester Tethered Systems

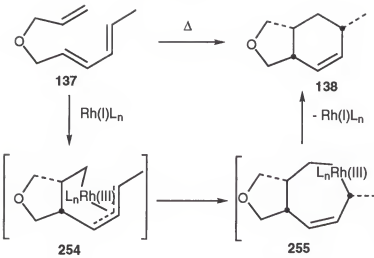
As discussed in the historical section, we wanted to expose model triene **189**, successfully cyclized under thermal conditions, to some alternative cyclization conditions. In addition, we wanted to prepare an ester tethered system analogous to ether tetethered triene **189** in order to compare the reactivity of the ether and ester systems. After obtaining the results, we would compare the observations to previous examples from the literature.

Alternative Conditions for the Ether Tethered Triene

In an effort to further understand the reactivity of three atom oxygen tethered nonatriene intramolecular cycloadditions, the ether tethered Diels-Alder precursor **189** was subjected to some alternative cyclization conditions. The goal was to determine if either the yield or stereoselectivity could be affected by altering the reaction conditions.

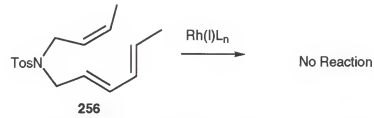
After examining triene **189**, we decided that the best alternative conditions for this cyclization would be that of transition metal catalysis. As discussed previously in the historical section, Livinghouse[56] effectively cyclized a variety of nonatrienes with a central oxygen atom in the tether. The mechanism as shown by Livinghouse proceeds via a Rhodium metallacycle resulting in high yielding cyclizations with excellent diastereoselctivity (Scheme 85). However, the reaction was sometimes not possible when more highly substituted alkenes were subjected to the cyclization conditions. For example,

Scheme 85



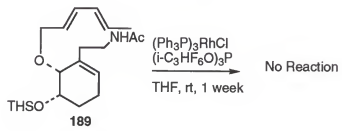
Livinghouse reported that when a cyclization was attempted with the *cis*-substituted nonatriene **256** the starting material was recovered without observation of any cycloadducts (Scheme 86).[98] We wanted to subject our triene to analogous conditions in order to confirm this observation.

Scheme 86



Returning to the previously synthesized nonatriene **189**, we attempted the cyclization in the presence of $(Ph_3P)_3RhCl$ and $(i\text{-}C_3HF_6O)_3P$ in THF (Scheme 87). After

Scheme 87



stirring for 1 week at room temperature, no products were observed and the starting material remained unaffected. We therefore ruled out transition metal catalysis as a means of facilitating the intramolecular Diels-Alder reaction of this substrate.

We were also interested in subjecting triene **189** to microwave conditions. After dissolving the starting triene **189** in toluene, the reaction mixture was placed in a screw capped vial and heated in a microwave oven at 2 minute intervals. After three intervals, no reaction or decomposition of starting material was observed. Finally, after heating twice at 5 minute intervals, still no degradation or reaction had occurred. We concluded that microwave conditions were not effective.

Despite the available alternative conditions for the intramolecular Diels-Alder reaction, we were unable to find any which compared in effectiveness to the standard thermal conditions. While the transition metal catalysis method appeared promising, the steric demand of triene **189** was not compatible with the requirements of the rhodium catalyst. We did not attempt Lewis acid catalysis because our triene system did not contain a carbonyl functional group. Without the carbonyl, the Lewis acid would not be able to coordinate to the triene and the electronics of the triene system would thus not be affected. Finally, we were unable to cyclize or degrade the starting triene **189** under microwave conditions. We concluded that, with this ether tethered system, heating was the best method for inducing the [4+2] cycloaddition.

Ester Tethered Triene Systems

An extension of the second generation Diels-Alder approach was to compare the reactivity of an analogous ester tethered system both in reactivity and stereochemical outcome. Based on previous examples, ester tethered systems, although electronically more activated, often are unable to adopt the proper orbital alignment necessary for a Diels-Alder reaction to occur. It has been well documented that esters exist nearly completely in the *s-trans* conformation due to dipole repulsion,[99] but as described previously in Chapter 2, IMDA reactions of ester trienes are known.[76,77,79] If a Diels-Alder adduct containing an

ester functional group were obtained, it would contain a functional handle which could possibly lead to incorporation of the aromatic ring necessary for the complete morphine skeleton (Figure 15). If adducts similar to **258** are obtainable, closure and isomerization of the double bond into conjugation with the carbonyl would afford an enone **257** which could undergo 1,4-conjugate additions and be further manipulated.

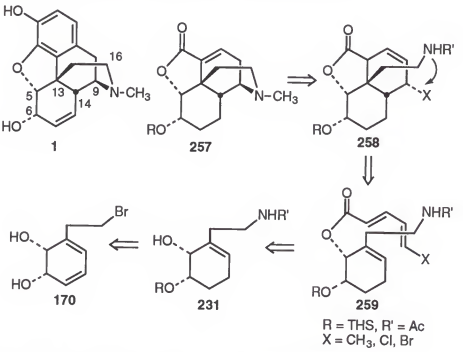
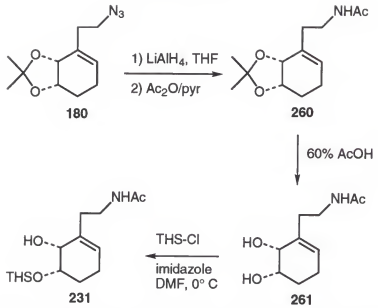


Figure 15. Retrosynthetic plan for ester model system

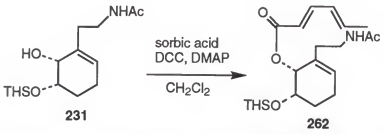
With this retrosynthetic plan we set out to provide the model ester tethered triene **259** where X = CH_3. The best method for constructing the desired ester triene system would be via a condensation of sorbic acid with an appropriate alcohol. For the desired ester synthesis, we sought an efficient route to acetamide **231** (Scheme 88). The previously synthesized azide **180** was readily reduced by $LiAlH_4$ to give the crude amine which was directly protected by stirring in pyridine / acetic anhydride to yield acetamide **260**. Cleavage of the isopropylidene was achieved by stirring acetamide **260** in 60% acetic acid to afford diol **261**. The diol was then protected at the least hindered homoallylic hydroxyl exclusively to give thexyldimethylsilyl ether **231**. Subjecting the

Scheme 88



the alcohol to DCC condensation with sorbic acid over a prolonged period gave a poor yield of the desired ester **262** (Scheme 89). The poor yield was attributed to a heavily congested reaction site which was compounded by the bulk of the activated DCC complex.

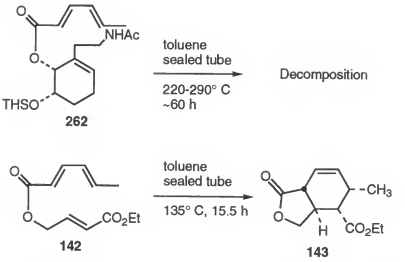
Scheme 89



The resulting ester **262** was subjected to the identical thermal conditions utilized in the cyclization of the analogous ether tethered triene **189** described previously in section one of this chapter. After heating in toluene in a sealed tube at 220° C for 18 hours, no disappearance of the starting material or formation of any new products was observed by TLC. After an additional 19 hours at 245° C, no observable changes were noted. Finally, after pushing the reaction for another 24 hours at 290° C, the starting material decomposed and no interpretable products could be isolated (Scheme 90).

Although this was a disappointing result, by comparing triene **262** with a similar triene **142** prepared by Boeckman from sorbic acid and ethyl 4-bromocrotonate, some conclusions were made (Scheme 90).[77] We discovered that our system had two disadvantages when compared to diester **142**. First, triene **262** contains a trisubstituted unactivated dienophile which is electronically less reactive than the ester activated dienophile of diester **142**. The second problem was that the dienophile was part of a six

Scheme 90



member ring which placed further steric requirements on the IMDA reaction. While the flexible activated diester triene **142** cyclized at 135° C, we were unable to overcome the steric problems and unfavorable electronics and reached the thermal decomposition temperature of triene **262** before any cyclization was observed.

The most important conclusion from the cyclization attempt on ester **262** is apparent when its reactivity was compared to the successful ether triene **189**. As demonstrated by the work of Burke[73] and Funk,[74] previously discussed in Chapter 2, when unactivated dienophiles were tethered by an ester linkage, no IMDA adducts were isolated. However, when the linkage was switched to a simple ether, the reactions were successful. Our investigation afforded the identical results found in these literature examples. We were not able to place the ester in the necessary *s-cis* configuration under thermal conditions, but the unrestricted ether linkage cyclized readily to the desired Diels-Alder adduct. This

investigation was supported by literature precedent and provided an additional example of the contrast in reactivity between ether and ester tethered nonatrienes.

CHAPTER 4
CONCLUSIONS

Summary

The most important result in this dissertation was the synthesis and stereochemical proof of an advanced tricyclic morphine fragment which contained all 5 of the chiral centers found in natural (-)-morphine in the correct absolute stereochemistry. This was achieved through a chemoenzymatic synthesis which combined microbial dihydroxylation with a stereospecific intramolecular Diels-Alder cycloaddition strategy. The results of the advanced model moved us to repeat the chemistry reported in the previously published intramolecular Diels-Alder study. Through repetition of the chemistry and analogous X-ray crystallography of the free alcohol, we established the stereochemistry of the previous Diels-Alder adduct and subsequently submitted this result as a formal structure correction.

After obtaining a better understanding of the stereochemical outcome of the intramolecular Diels-Alder reaction, attempts at synthesizing a higher ordered morphinan were made. While these attempts did not result in the desired outcome, we were able to find literature proof which provided justification for the observations.

Finally, we studied the intramolecular Diels-Alder reaction under some varied conditions and were also able to compare the reactivity of ether and ester tethered triene systems. The observed results of the comparison matched with those found in the literature and thus provided another example of the differing reactivity of these triene systems.

Future Investigations

Clearly, as described previously, the steric requirements in the transition state of the intramolecular Diels-Alder cycloaddition determine the stereochemical outcome of the

reaction. There are three modifications of the reported triene system which could provide additional insight on these steric requirements: 1) decrease the size of the substituent at C_6, 2) oxidize the C_6 hydroxyl to a ketone, or 3) attempt the cycloaddition with a stable *E,Z*-diene. Such modifications would allow for a more reliable method of predicting the stereochemical outcome of the cycloaddition.

The first modification would be to remove the large thexyldimethylsilyl protecting group to give triene **263** and determine if the free alcohol undergoes the identical *exo* cycloaddition (Figure 16). The free alcohol would be sterically less demanding than the

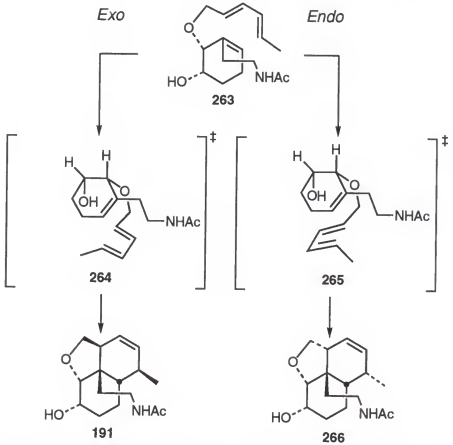


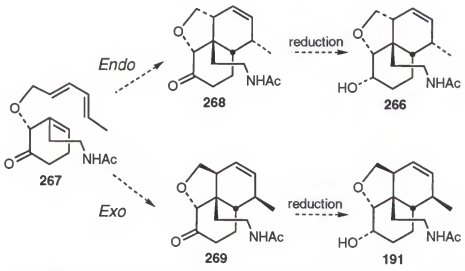
Figure 16. Transition states for the free hydroxyl model system

thexyldimethylsilyl group and might allow for the cyclization to proceed via the *endo* transition state **265**. If the reaction proceeds via the *exo* transition state **264** we would isolate the previous tricycle **191**. Isolation of the *endo* cycloadduct **266** would suggest

that by manipulating the protecting group at the C_6 stereocenter, we would have routes to either adduct.

A second more severe tactic would be to oxidize the C_6 hydroxyl to ketone **267** prior to the cyclization (Scheme 91). Although this would remove a chiral center provided by the microbial dihydroxylation, it would convert the C_6 to an sp^2 center and completely remove any steric influences that the alcohol (protected or free) may have on the Diels-Alder transition state. By removing this distant influence, a clearer understanding of the steric requirement of the tethered diene and cyclohexene dienophile would result and provide a predictive model for the design of future systems. Chirality could be reinstalled after the cycloadduct is isolated by selective reduction, which would occur from the less hindered β-face of the molecule.

Scheme 91



A third idea would be to synthesize the analogous *E,Z*-diene **270**, a derivative of the previously successful ether tethered triene **189** (Figure 17). If the cycloaddition occurs via the *exo* transition state **271** as observed in the previous cycloaddition, the terminal methyl of *E,Z*-diene **270** would point directly toward the thexyl protecting group. An unfavorable steric interaction such as this may cause the *endo* transition state **272** to be more favorable and could afford cycloadduct **274** with the opposite stereochemical

outcome to that observed previously. Understanding the stereochemical outcome of the cyclization of this model *E,Z*-diene system would provide necessary insight for the design of advanced model systems bearing a terminal leaving group.

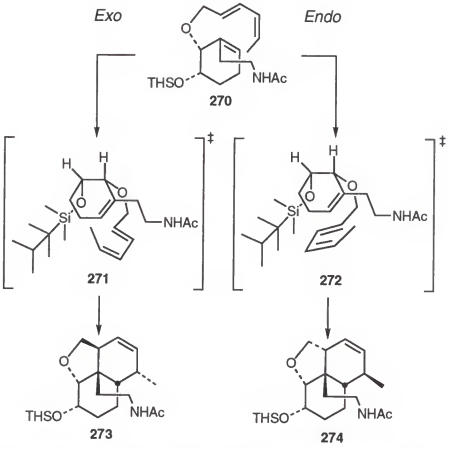
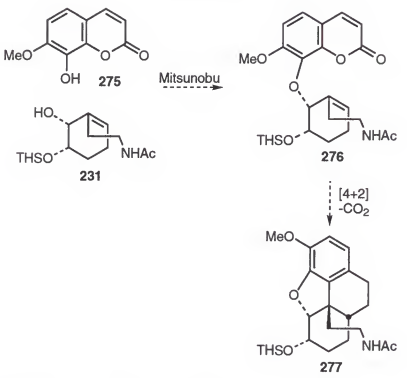


Figure 17. Transition states for *E,Z*-methyl diene model system

A more important consideration for application of this methodology toward the pursuit of a total morphine synthesis is to find a means of incorporating the aromatic A ring, a necessary requirement for biological activity, into triene system (Scheme 92). By synthesizing a tethered coumarin precursor **276**, obtained from a double Mitsunobu inversion of acetamide **231** with methoxyhydroxy coumarin **275**, one can predict a cyclization followed by CO_2 extrusion to afford cycloadduct **277**. As discussed in the historical section, Ciganek utilized a similar extrusion of CO_2 to drive the cyclization to

completion.[80] Ether **276** would have both the CO_2 extrusion and rearomatization of the cycloadduct as irreversible driving forces toward the phenanthrene **277**. Although the D ring closure would not be dierectly possible in phenanthrene **277**, this adduct may alone have interesting biological properties.

Scheme 92

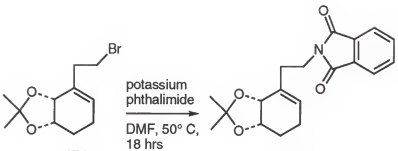


Investigation of methods for incorporating the aromatic ring into this methodology would require significant effort, but this could provide the synthetic community with an efficient method for stereospecifically constructing interesting and potentially biologically active morphinans. While the pursuit of an efficient total synthesis of morphine still eludes the synthetic community, we hope that the findings and projections described in this dissertation will contribute to the continuing effort.

CHAPTER 5
EXPERIMENTAL

General Procedures and Instrumentation

All non-hydrolytic reactions were performed under an atmosphere of argon in solvents either dried according to standard procedures or purchased from Aldrich. Analytical TLC was performed on silica gel 60F-254 (Whatman) plates. Flash column chromatography was performed on Fisher silica gel (grade 60, 200-425 mesh). ^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR-300 MHz instrument in d-chloroform unless otherwise indicated. The 2D TOCSY NMR experiment was performed on a Varian Unity 500 MHz instrument. All ^{13}C multiplicities were determined by APT experiments. Mass spectra were recorded on a Finnigan Mat 95 Q mass spectrometer. IR spectra were obtained on a Perkin Elmer 1600 Series instrument. X-ray crystallographic data was obtained on a Siemens SMART Platform equipped with a CCD area detector. Optical rotations were measured on a Perkin Elmer polarimeter. Combustion analyses were performed by Atlantic Microlabs, Inc. Melting points were measured on a Unimelt apparatus.



174 175

(3a*S*,7a*R*)-2,2-Dimethyl-4-[2-(phthalimido)ethyl]-4,5-dihydrobenzo[d][1,3]dioxole (175):

To a solution of bromide **174** (375 mg, 1.44 mmol) in DMF (6 mL) was added potassium phthalimide (399 mg, 2.15 mmol). The reaction mixture was warmed to 50° C and stirred for 18 h. Water (60 mL) was added and the crude product was extracted into ethyl acetate (5x 15 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by column chromatography (7:3 hexanes/ethyl acetate) to obtain phthalimide **175** (446 mg, 95%) as a colorless oil; R_f = 0.39 (7:3 hexane/ethyl acetate); $[\alpha]_D^{26}$ + 84.2 (c = 1.00, $CHCl_3$).

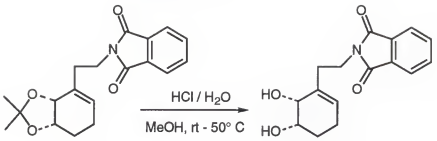
Found: C, 69.47; H; 6.53, N, 4.27. ($C_{19}H_{21}NO_4$) requires: C, 69.71; H, 6.47; N, 4.28%.

IR ($CHCl_3$): ν = 2980, 2930, 1770, 1710, 1610, 1390 cm^{-1}

^1H NMR: δ = 7.78 (m, 2H), 7.68 (m, 2H), 5.52 (s, 1H), 4.55 (d, J = 5.6 Hz, 1H), 4.30 (m, 1H), 3.93 (m, 1H), 3.74 (m, 1H), 2.46 (m, 2H), 2.08 (m, 1H), 1.72 (m, 3H), 1.36 (s, 3H), 1.32 (s, 3H).

^{13}C NMR: δ = 168.2 (C), 133.8 (CH), 132.9 (C), 127.7 (CH), 123.0 (CH), 108.3 (C), 73.2 (CH), 72.8 (CH), 36.4 (CH_2), 32.8 (CH_2), 27.7 (CH_3), 26.4 (CH_3), 25.2 (CH_2), 20.6 (CH_2).

MS (CI/methane): *m/z* = 328 ($M+H^+$, 10%), 270 (100), 252 (30).



175 176

(1*S*,2*R*)-3-[2-(Phthalimido)ethyl]-3-cyclohexene-1,2-diol (176):

To a solution of acetonide **175** (1.75 g, 5.20 mmol) in MeOH (8 mL) was added concentrated hydrochloric acid (0.1 mL) and water (0.1 mL). The reaction mixture was stirred at rt for 1 h and then heated to 50° C over an additional 2 h. The solvent was removed at reduced pressure and the crude product was purified by column chromatography (1:1 hexanes/ethyl acetate) to afford diol **176** (1.24 g, 84%) as white crystals; mp 111-113° C; R_f = 0.13 (1:1 hexanes/ethyl acetate); $[\alpha]_D^{26}$ - 120.8 (c = 1.0, $CHCl_3$).

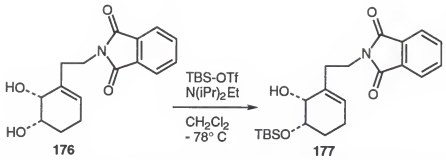
Found: C, 66.98; H, 5.91; N, 4.69. ($C_{16}H_{17}NO_4$) requires: C, 66.89; H, 5.96; N, 4.88%.

IR (KBr): ν = 3420, 2940, 1770, 1710, 1390, 1030 cm^{-1}.

^{1}H NMR: δ = 7.82 (dd, J = 3.0, 5.6 Hz, 2H), 7.71 (dd, J = 3.1, 5.4 Hz, 2H), 5.40 (bs, 1H), 4.10 (d, J = 3.7 Hz, 1H), 3.90 (m, 2H), 3.68 (dt, J = 10.8, 3.9 Hz, 1H), 2.82 (bs, 2H), 2.44 (m, 2H), 1.80 (bs, 2H), 1.62 (m, 2H).

^{13}C NMR: δ = 168.8 (2x C), 134.1 (2x C), 133.8 (2x C), 131.9 (C), 129.1 (CH), 123.3 (2x CH), 69.5 (CH), 69.4 (CH), 37.7 (CH_2), 34.9 (CH_2), 25.1 (CH_2), 24.1 (CH_2).

MS (EI): *m/z* = 288 ($M+H^+$, 25%), 270 (100), 252 (20), 160 (40), 123 (83).



176 177

(5*S*,6*R*)-N-[2-(5-(1,1-Dimethylethyl)dimethylsiloxy)-6-hydroxy-1-ene-1-yl) ethyl]phthalidimide (177):

To a precooled (-78° C) solution of diol **176** (191 mg, 0.67 mmol) in CH_2Cl_2 (50 mL) and $N(iPr)_2Et$ (173 mg, 233 μL, 1.34 mmol) was added dropwise TBDMS-OTf (212 mg, 185 μL, 0.80 mmol). The reaction mixture was stirred for 1 h and quenched with water (5 mL). The crude product was extracted into CH_2Cl_2 (4x 25 mL). The combined organic phases were dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude product was purified by column chromatography (7:3 hexanes/ethyl acetate) to afford silyl ether **177** (261 mg, 87%) as a colorless oil; $R_f = 0.69$ (1:1 hexanes/ethyl acetate); $[\alpha]_D^{26}$ + 11.4 (c = 1.09, $CHCl_3$).

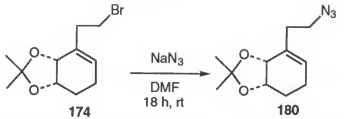
IR ($CHCl_3$): ν = 3550, 2960, 1740, 1470, 1370, 1250, 1090 cm^{-1}.

^1H NMR: δ = 7.82 (dd, J = 5.5, 3.0 Hz, 2H), 7.69 (dd, J = 5.5, 3.0 Hz, 2H), 5.47 (bs, 1H), 4.05 (d, J = 3.8 Hz, 1H), 3.88 (m, 1H), 3.79 (m, 2H), 2.48 (m, 2H), 2.06 (m, 1H), 1.78 (m, 2H), 1.50 (m, 1H), 0.92 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H).

^{13}C NMR: δ = 168.2 (C), 134.1 (C), 133.8 (CH), 132.0 (C), 127.6 (CH), 123.0 (CH), 70.6 (CH), 68.2 (CH), 36.8 (CH_2), 33.6 (CH_2), 25.8 (CH_3), 25.4 (CH_2), 23.9 (CH_2), 18.1 (C), - 4.6 (CH_3), - 4.8 (CH_3).

MS (FAB): *m/z* = 402 ($M+H^+$, 15%) 384 (100), 344 (30), 197 (20).

HRMS: 402.2135, ($C_{22}H_{32}NO_4Si+H$) requires, 402.2100.



(3a*S*,7a*R*)-7-(2-Azidoethyl)-2,2-dimethyl-4,5-dihydrobenzo[1,3]dioxole (180):

To a solution of bromoacetonide **174** (2.8 g, 10.7 mmol) in DMF (30 mL) was added NaN_3 (2.74 g, 42.13 mmol). The reaction mixture was stirred at rt for 18 h, and then cooled (0° C) and water (100 mL) was added. The crude product was extracted into diethyl ether (3x 25 mL), and the combined organic phases were washed with brine (2x 25 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure to give azide **180** (2.38 g, 99%) as a pale yellow oil, which required no further purification; R_f = 0.18 (95:5 hexanes/ethyl acetate); $[\alpha]_D^{25}$ + 32.7 (c = 1.17, $CHCl_3$).

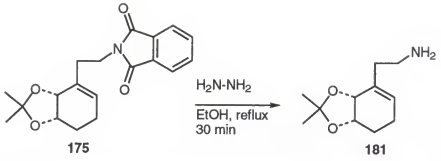
Found: C, 59.31; H, 7.76; N, 18.74. ($C_{11}H_{17}N_3O_2$) requires: C, 59.17; H, 7.67; N, 18.82%.

IR ($CHCl_3$): ν = 2985, 2930, 2095, 1240, 1220 cm^{-1}.

^1H NMR: δ = 5.71 (bs, 1H), 4.36 (d, J = 5.6 Hz, 1H), 4.32 (m, 1H), 3.42 (t, J = 7 Hz, 2H), 2.40 (m, 2H), 2.18 (m, 1H), 1.89 (m, 2H), 1.73 (m, 1H), 1.37 (s, 6H).

^{13}C NMR: δ = 132.4 (C), 127.8 (CH), 108.5 (C), 73.6 (CH), 73.4 (CH), 49.6 (CH_2), 33.6 (CH_2), 27.9 (CH_3), 26.5 (CH_3), 25.3 (CH_2), 20.7 (CH_2).

MS (CI): *m/z* = 224 ($M+H^+$, 28%), 166 (12), 138 (82), 120 (100).



175 181

(3a*R*,7a*S*)-2,2-Dimethyl-4-[2-(aminoethyl)]-3a,6,7,7a-tetrahydrobenzodioxol (181):

To a solution of phthalimide **175** (348 mg, 1.06 mmol) in EtOH (10 mL) was added hydrazine (0.5 mL, 15.9 mmol). The reaction mixture was heated at reflux for 30 min. A thick white precipitate was observed. The mixture was cooled to - 4° C over 30 min. and filtered and the solid was rinsed with CH_2Cl_2. The filtrate was treated with 10% citric acid (3x 5 mL) to remove the crude product. The combined aqueous phases were treated with sodium bicarbonate until the pH = 9. The crude amine was then extracted into CH_2Cl_2 (3x 15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The amine **181** (171 mg, 82%) was isolated as a colorless oil and required no further purification; R_f = 0.53 (7:3:1 ethyl acetate/ethanol/water); $[\alpha]_D^{25}$ + 31.1 (c = 1.00, $CHCl_3$).

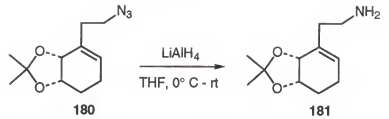
IR ($CHCl_3$): ν = 3360, 2930, 1570, 1380, 1240, 1220, 1080, 1060, 1030 cm^{-1}.

^1H NMR: δ = 5.61 (bs, 1H), 4.30 (d, J = 5.6 Hz, 1H), 4.24 (m, 1H), 2.79 (m, 2H), 2.30 (m, 1H), 2.13 (m, 2H), 1.80 (m, 3H), 1.41 (s, 2H), 1.34 (s, 3H), 1.32 (s, 3H).

^{13}C NMR: δ = 133.6 (C), 126.8 (CH), 108.2 (C), 73.5 (CH), 73.4 (CH), 38.4 (CH_2), 27.9 (CH_3), 26.4 (CH_3), 25.5 (CH_2), 20.8 (CH_2).

MS (CI/methane): *m/z* = 198 ($M+H^+$, 100%).

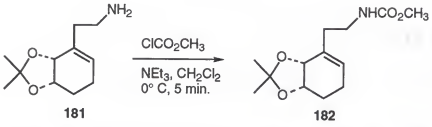
HRMS: 198.1519, ($C_{11}H_{19}NO_2$+H) requires, 198.1494.



180 **181**

(3a*R*,7a*S*)-2,2-Dimethyl-4-[2-(aminoethyl)]-3a,6,7,7a-tetrahydrobenzodioxol (181):

To a precooled (0° C) solution of $LiAlH_4$ (40 mg, 1.06 mmol) in THF (20 mL) was added dropwise a solution of azide **180** (237 mg, 1.06 mmol) in THF (5 mL). The cooling bath was removed and the reaction mixture was stirred for 3 h. The mixture was cooled (0° C) and quenched with water (1 mL), followed by 10% NaOH (2 mL) and finally water (1 mL). The lithium salts were removed be filtration, and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (7:3:1 ethyl acetate/ethanol/ammonium hydroxide) to give amine **181** (140 mg, 67%) as a yellow oil.



181 **182**

(3a*S*,7a*R*)-2,2-Dimethyl-7-[2-(N-methylcarbamoyl)ethyl]-4,5-dihydrobenzo [d][1,3]dioxole (182):

To a solution of amine **181** (143 mg, 0.727 mmol) in CH_2Cl_2 (8 mL) was added NEt_3 (300 µL, 2.181 mmol). The reaction mixture was cooled (0° C) and methylchloroformate (62 µL, 0.800 mmol) was added dropwise via syringe. The mixture was stirred vigorously for 5 min. The solvent was removed at reduced pressure and the crude product was purified by column chromatography (1:1 hexanes/ethyl acetate) to give carbamate **182**

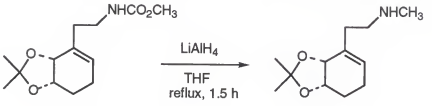
(160 mg, 86%) as a colorless oil; R_f = 0.43 (1:1 hexanes/ethyl acetate); $[\alpha]_D^{25}$ + 21.1 (c = 1.0, $CHCl_3$).

Found: C, 61.10; H, 8.55; N, 5.47. ($C_{13}H_{21}NO_4$) requires: C, 61.16; H, 8.29; N, 5.49%.

IR ($CHCl_3$): ν = 3340, 3000, 2930, 1705, 1540, 1240, 1080 cm^{-1}.

^1H NMR: δ = 5.66 (bs, 1H), 4.98 (bs, 1H), 4.32 (d, J = 5.9 Hz, 1H), 4.28 (m, 1H), 3.62 (s, 3H), 3.31 (dd, J = 12.2, 5.6 Hz, 2H), 2.38 (m, 1H), 2.17 (m, 2H), 1.79 (m, 3H), 1.38 (s, 3H), 1.36 (s, 3H)

^{13}C NMR: δ = 156.8 (C), 132.9 (C), 127.7 (CH), 108.0 (C), 73.3 (CH), 73.2 (CH), 51.7 (CH_3), 39.2 (CH_2), 34.5 (CH_2), 27.6 (CH_3), 26.1 (CH_3), 25.4 (CH_2), 20.6 (CH_2).
MS (CI, methane): *m/z* = 256 ($M+H^+$, 19%), 198 (100), 180 (18), 166 (32), 123 (32).



182 **183**

(3a*s*,7a*R*)-2,2-Dimethyl-7-[2-(N-methylamino)ethyl]-4,5-dihydrobenzo[d][1,3]dioxole (183):

To a solution of carbamate **182** (272 mg, 1.07 mmol) in THF (20 mL) was added $LiAlH_4$ (85 mg, 2.13 mmol). Gas evolution was observed, and the reaction mixture was heated at reflux for 1.5 h. After cooling to rt, the mixture was quenched with water (0.08 mL), then 10% NaOH (0.08 mL), and last another portion of water (0.24 mL). The gray lithium salts were removed by filtration, rinsing the residue thoroughly with ethyl acetate, and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (7:3:1 ethyl acetate/ethanol/ammonium hydroxide) to afford amine **183**

(89 mg, 40%) as a yellow oil; R_f = 0.68 (7:3:1 ethyl acetate/ethanol/ammonium hydroxide); $[\alpha]_D^{28}$ + 29.7 (c=1.15, $CHCl_3$).

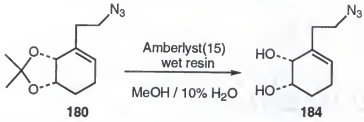
IR ($CHCl_3$): ν = 3320, 2980, 2930, 1650, 1440, 1380, 1240, 1220, 1160, 1070, cm^{-1}.

^1H NMR: δ = 5.64 (bs, 1H), 4.34 (d, J = 5.8 Hz, 1H), 4.28 (m, 1H), 2.71 (t, J = 6.8 Hz, 2H), 2.42 (s, 3H), 2.35 (m, 1H), 2.28 (m, 1H), 2.16 (m, 1H), 1.95-1.80 (m, 2H), 1.77-1.66 (m, 2H), 1.37 (s, 3H), 1.36 (s, 3H).

^{13}C NMR: δ = 133.7 (C), 1276.4 (CH), 108.0 (C), 73.4 (CH), 73.2 (CH), 49.5 (CH_2), 36.0 (CH_3), 34.0 (CH_2), 27.6 (CH_3), 26.2 (CH_3), 25.3 (CH_2), 20.6 (CH_2).

MS (FAB): *m/z* = 212 ($M+H^+$, 100%), 172 (45), 132 (55).

HRMS: 212.1641, ($C_{12}H_{21}NO_2$+H) requires, 212.1650.



180 **184**

(1*S*,2*R*)-3-(2-Azidoethyl)-3-cyclohexene-1,2-diol (184):

To a solution of azide **180** (146 mg, 0.65 mmol) in MeOH (5 mL) was added water (0.5 mL) followed by Amberlyst (15) wet ion exchange resin (450 mg). The reaction mixture was stirred at rt for 14 h. After removal of the resin by filtration, the solvent was removed under reduced pressure with benzene being added to azeotrope the residual water. The crude product was purified by column chromatography (1:1 hexanes/ethyl acetate) to give diol **184** (110 mg, 92%) as white crystals; mp 54-55° C; R_f = 0.13 (1:1 hexanes/ethyl acetate); $[\alpha]_D^{29}$ - 98.5 (c = 1.0, $CHCl_3$).

Found: C, 52.47; H, 7.09; N, 22.78. ($C_8H_{14}O_2N_3$) requires: C, 52.43; H, 7.16; N, 22.94%.

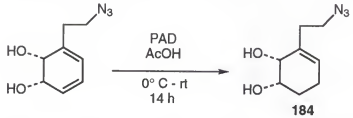
IR (KBr): ν = 3550, 2950, 2095, 1460, 1370, 1250, 1080 cm^{-1}.

^1H NMR: δ = 5.66 (bs, 1H), 3.99 (d, J = 3.4 Hz, 1H), 3.75 (m, 1H), 3.40 (t, J = 7 Hz, 2H), 2.96 (s, 2H), 2.40 (m, 2H), 2.16 (m, 1H), 2.08 (m, 1H), 1.70 (m, 2H).

^{13}C NMR: δ = 133.9 (C), 128.1 (CH), 69.5 (CH), 68.6 (CH), 50.1 (CH_2), 34.0 (CH_2), 25.1 (CH_2), 23.9 (CH_2).

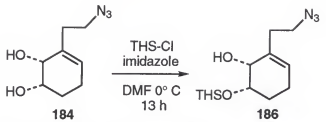
MS (EI): *m/z* = 184 (M^+, 8%), 138 (42), 120 (100).

HRMS: 184.1153, ($C_8H_{14}O_2N_3$+H) requires, 184.1086.



184

To a solution of azidodienediol (~35 g, 0.19 mol) in methanol (300 mL) was added potassium azodicarboxylate (PAD, 85 g, 0.44 mol). The suspension was cooled to 0° C, and a mixture of acetic acid (50 mL) and methanol (100 mL) was added dropwise over 2 h. The solution was allowed to warm to rt and continued stirring for 14 h. Additional acetic acid (10 mL) was added to react with any excess PAD, and the mixture was concentrated by rotary evaporation. Water (150 mL) was added and the crude product was extracted into CH_2Cl_2 (5x 50 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The remaining solid was recrystallized (CH_2Cl_2/hexanes) to afford diol **184** (25 g, 72%) as a white crystalline material.



(1*R*,6*S*)-2-(2-Azidoethyl)-6-(thexyldimethylsiloxy)-2-cyclohexen-1-ol (186):

To a cooled (0° C) solution of diol **184** (122 mg, 0.67 mmol) in DMF (0.75 mL) was added imidazole (54 mg, 0.80 mmol) followed by thexyldimethylsilyl chloride (142 mg, 0.80 mmol). The mixture was stirred briefly and allowed to stand at 0° C for 13 h. Water (40 mL) was added and the aqueous layer was extracted with diethyl ether (3x 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by column chromatography (9:1 hexane/ethyl acetate) to afford silyl ether **186** (214 mg, 99%) as a colorless oil; R_f = 0.49 (9:1 hexane/ethyl acetate); $[\alpha]_D^{26}$ -37.0 (c = 1.2, $CHCl_3$).

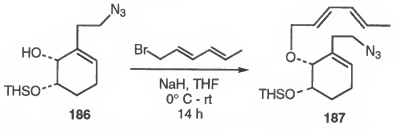
Found: C, 59.11; H, 9.64; N, 12.84. ($C_{16}H_{31}O_2N_3Si$) requires: C, 59.04; H, 9.60; N, 12.91%.

IR ($CHCl_3$): ν = 3550, 2950, 2095, 1460, 1370, 1250, 1080 cm^{-1}.

^1H NMR: δ = 5.65 (bs, 1H), 3.89 (bs, 1H), 3.81 (dt, J = 10.7, 3.9 Hz, 1H), 3.41 (m, 2H), 2.66 (d, J = 2.7 Hz, 1H), 2.42 (m, 2H), 2.17 (m, 1H), 2.02 (m, 1H), 1.77 (m, 1H), 1.63 (sept, J = 6.9 Hz, 1H), 1.55 (m, 1H), 0.89 (d, J = 6.9 Hz, 3H), 0.88 (d, J = 6.9 Hz, 3H), 0.85 (s, 6H), 0.14 (s, 3H), 0.13 (s, 3H).

^{13}C NMR: δ = 133.7 (C), 127.6 (CH), 70.8 (CH), 68.8 (CH), 50.0 (CH_2), 34.5 (CH_2), 34.2 (CH), 25.3 (CH_2), 24.9 (C), 24.1 (CH_2), 20.3 (CH_3), 20.2 (CH_3), 18.6 (CH_3), 18.5 (CH_3), - 2.4 (CH_3), - 3.0 (CH_3).

MS (EI): *m/z* = 308 ($M-H_2O^+$, 45%), 280 (100).



(5*S*,6*R*)-(2*E*,4*E*)-1-(2-Azidoethyl)-6-(2,4-hexadienyloxy)-5-(thexyldimethylsiloxy)-1-cyclohexene (187):

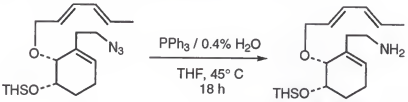
To a cooled (0° C) suspension of sodium hydride (117 mg, 2.92 mmol, 60% in mineral oil) in THF (1 mL) was added dropwise a solution of the azidoalcohol **186** (476 mg, 1.46 mmol) in THF (2 mL). The mixture stirred at 0° C for 20 min. A solution of sorbyl bromide (353 mg, 2.19 mmol) in THF (1 mL) was added dropwise. The cooling bath was removed and the mixture was stirred for 14 h. Water (70 mL) was added and the crude product was extracted into diethyl ether (3x 30 mL). The combined organic layers were washed with brine and dried ($MgSO_4$). Removal of solvent under reduced pressure gave a crude product which was purified by repeated column chromatography (99:1 hexane/ethyl acetate) [Note: Three separate columns were necessary to separate the product from unreacted sorbyl bromide.] to afford ether **187** as a pale yellow oil (344 mg, 58%); R_f = 0.61 (95:5 hexane/ethyl acetate); $[\alpha]_D^{26}$ - 53.2 (c = 1.11, $CHCl_3$).

IR ($CHCl_3$): ν = 2950, 2870, 2095, 1460, 1380, 1250, 1100 cm^{-1}.

^1H NMR: δ = 6.17 (dd, J = 14.8, 10.2 Hz, 1H), 6.05 (ddd, J = 14.7, 10.4, 1.7 Hz, 1H), 5.68 (m, 2H), 5.55 (bs, 1H), 4.46 (dd, J = 12.1, 5.8 Hz, 1H), 4.09 (dd, J = 12.1, 7.1, 1H), 3.82 (dt, J = 11.0, 3.0 Hz, 1H), 3.64 (d, J = 3.0 Hz, 1H), 3.33 (m, 2H), 2.34 (m, 2H), 2.18 (m, 1H), 2.03 (m, 1H), 1.90 (m, 1H), 1.75 (d, J = 6.6 Hz, 3H), 1.66 (sept, J = 6.8 Hz, 1H), 1.58 (m, 1H), 0.91 (s, 3H), 0.89 (s, 3H), 0.86 (s, 3H), 0.85 (s, 3H), 0.12 (s, 6H).

^{13}C NMR: δ = 133.5 (C), 133.0 (CH), 130.9 (CH), 129.8 (CH), 127.7 (CH), 127.3 (CH), 76.9 (CH), 73.0 (CH_2), 71.9 (CH), 50.2 (CH_2), 34.1 (CH_2), 34.0 (CH_3), 25.7 (CH_2), 24.9 (C), 24.8 (CH_2), 20.3 (2x CH_3), 18.6 (CH_3), 18.1 (CH_3), - 2.6 (2x CH_3).

HRMS: 406.2824, ($C_{22}H_{39}O_2N_3Si$+H) requires, 406.2889.



187 **188**

(5*S*,6*R*)-(2*E*,4*E*)-1-(2-Aminoethyl)-6-(2,4-hexadienyloxy)-5-(thexyldimethylsiloxy)-1-cyclohexene (188):

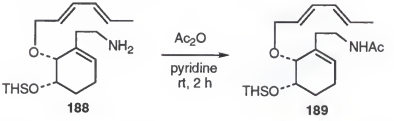
To a solution of azide **187** (106 mg, 0.26 mmol) in THF (10 mL) was added triphenylphosphine (102.8 mg, 0.39 mmol) and water (0.04 mL). After stirring at 45° C for 18 h, the mixture was concentrated under reduced pressure and the crude product was purified by column chromatography (ethyl acetate-50% saturated with ammonium hydroxide) [Note: The eluent was prepared by diluting ethyl acetate fully saturated with ammonium hydroxide with an equal volume of 100% ethyl acetate.] to afford the amine **188** as a pale yellow oil (65 mg, 66%); R_f = 0.71 (7:3:1 ethyl acetate/ethanol/ ammonium hydroxide); $[\alpha]_D^{28}$ - 72.5 (c = 1.22, $CHCl_3$).

IR ($CHCl_3$): ν = 3020, 2960, 2870, 1220, 1090 cm^{-1}.

^1H NMR: δ = 6.15 (dd, J = 14.9, 10.5 Hz, 1H), 6.05 (ddd, J = 14.4, 9.0, 1.5 Hz, 1H), 5.66 (m, 2H), 5.46 (s, 1H), 4.46 (dd, J = 12.5, 6.1 Hz, 1H), 4.08 (dd, J = 11.7, 6.8, 1H), 3.78 (dt, J = 11.2, 3.2 Hz, 1H), 3.58 (d, J = 2.7 Hz, 1H), 2.76 (m, 2H), 2.18 (m, 2H), 2.02 (m, 1H), 1.94 (m, 1H), 1.72 (d, J = 6.8 Hz, 3H), 1.66 (sept, J = 6.8 Hz, 1H), 1.57 (m, 1H), 1.38 (bs, 2H), 0.90 (s, 3H), 0.88 (s, 3H), 0.84 (s, 6H), 0.12 (s, 6H).

^{13}C NMR: δ = 134.7 (C), 132.7 (CH), 130.9 (CH), 129.5 (CH), 128.0 (CH), 126.3 (CH), 77.3 (CH), 73.2 (CH_2), 72.6 (CH), 40.4 (CH_2), 39.2 (CH_2), 34.0 (CH_3), 25.6 (CH_2), 25.0 (C), 24.9 (CH_2), 20.3 (CH_3), 20.2 (CH_3), 18.6 (CH_3), 18.5 (CH_3), - 2.6 (2x CH_3).

HRMS: 380.2977, ($C_{22}H_{41}O_2NSi$+H) requires, 380.2984.



188 189

(5*S*,6*R*)-(2*E*,4*E*)-1-(2-Acetamidoethyl)-6-(2,4-hexadienyloxy)-5-(thexyldimethylsiloxy)-1-cyclohexene (189):

To a solution of amine **188** (263 mg, 0.69 mmol) in pyridine (2 mL) was added acetic anhydride (106 mg, 1.04 mmol). The reaction mixture was stirred at rt for 2 h. The solvent was removed by rotary evaporation, and the crude product was purified by column chromatography (100% ethyl acetate) to afford the amide **189** (259 mg, 89%) as a colorless, viscous oil; R_f = 0.69 (ethyl acetate fully saturated with ammonium hydroxide); $[\alpha]_D^{28}$ -78.9 (c = 1.15, $CHCl_3$).

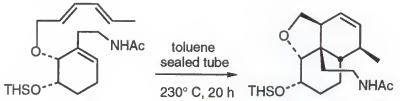
IR ($CHCl_3$): ν = 3450, 3020, 2980, 2900, 1660, 1520, 1220, 1050 cm^{-1}.

^1H NMR: δ = 6.18 (dd, J = 14.8, 10.2 Hz, 1H), 6.03 (ddd, J = 14.8, 10.4, 1.7 Hz, 1H), 5.67 (m, 2H), 5.51 (bs, 1H), 4.52 (dd, J = 11.8, 6.0 Hz, 1H), 4.05 (dd, J = 11.8, 7.0, 1H), 3.83 (dt, J = 10.7, 3.3 Hz, 1H), 3.61 (d, J = 2.8 Hz, 1H), 3.31 (m, 2H), 2.32 (m, 1H), 2.10 (m, 3H), 1.92 (m, 1H), 1.89 (s, 3H), 1.74 (d, J = 6.9 Hz, 3H), 1.64 (sept, J = 6.9 Hz, 1H), 1.56 (m, 1H), 0.89 (s, 3H), 0.88 (s, 3H), 0.84 (s, 6H), 0.12 (s, 3H), 0.11 (s, 3H).

^{13}C NMR: δ = 170.0 (C), 134.1 (C), 133.4 (CH), 130.8 (CH), 130.2 (CH), 127.4 (CH), 127.2 (CH), 77.9 (CH), 73.0 (CH_2), 71.9 (CH), 38.7 (CH_2), 34.3 (CH_2), 34.0 (CH_3), 25.8 (CH_2), 24.9 (C), 24.7 (CH_2), 23.3 (CH), 20.4 (CH_3), 20.2 (CH_3), 18.6 (CH_3), 18.5 (CH_3), - 2.6 (2x CH_3).

MS (FAB): *m/z* = 422 ($M+H^+$, 4%), 324 (86), 265 (98).

HRMS: 422.3056, ($C_{24}H_{43}O_3NSi$+H) requires, 422.3090.



189 **190**

(2a*S*,5*R*,5a*S*,8*S*,8a*R*,8b*S*)-8b-(2-Acetamidoethyl)-8-(dimethylthexylsiloxy)-5-methyl-2a,5,5a,6,7,8,8a,8b-octahydro-2H-benzoisobenzofuran (190):

A solution of triene **189** (126 mg, 0.299 mmol) in toluene (15 mL) was placed in a thick-wall glass reaction tube equipped with a Teflon screw cap. The reaction mixture was degassed using 3 repeated freeze-pump-thaw cycles, lowering the reaction tube's temperature to - 78° C at the start of each cycle, and sealed under an atmosphere of argon. The reaction tube was placed in a sand bath preheated to 230° C. After 20 h, the tube was cooled in a liquid nitrogen bath, carefully opened, and the contents removed. The toluene was removed under reduced pressure, and the crude product was purified by column chromatography (100% ethyl acetate) to afford the tricycle **190** (78 mg, 62%) as a colorless oil. Crystallization from hexanes afforded colorless crystals; mp 123-124° C; R_f = 0.21 (100% ethyl acetate); $[\alpha]_D^{26}$ + 11.0 (c = 1.0, $CHCl_3$).

Found: C, 67.85; H, 10.03; N, 3.24. ($C_{24}H_{43}NO_3Si$) requires: C, 68.36; H, 10.28; N, 3.32%.

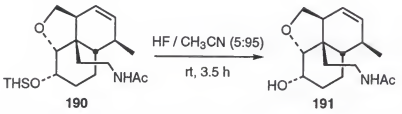
IR (KBr): ν = 3240, 2960, 2860, 1640, 1560, 1440, 1380, 1250, 1080 cm^{-1}.

^1H NMR: δ = 5.64 (dt, J = 9.6, 2.8 Hz, 1H), 5.57 (dt, J = 9.6, 2.8 Hz, 1H), 5.44 (bs, 1H), 4.10 (dd, J = 8.8, 6.9 Hz, 1H), 3.95 (t, J = 3.6 Hz, 1H), 3.71 (d, J = 5.2 Hz, 1H), 3.54 (dd, J = 11.5, 6.9 Hz, 1H), 3.42 (m, 1H), 3.29 (m, 1H), 3.12 (m, 1H), 1.94 (s, 3H), 1.90 (m, 1H), 1.64 (m, 5H), 1.44 (m, 1H), 1.27 (m, 2H), 1.14 (d, J = 7.7 Hz, 3H), 0.87 (d, J = 6.9 Hz, 6H), 0.83 (s, 6H), 0.12 (s, 3H), 0.08 (s, 3H).

^{13}C NMR: δ = 169.9 (C), 135.1 (CH), 123.2 (CH), 79.8 (CH), 68.6 (CH_2), 68.1 (CH), 45.9 (C), 42.7 (CH), 40.0 (CH), 37.4 (CH), 35.8 (CH_2), 34.0 (CH), 31.4 (CH_2), 30.1 (CH_2), 24.8 (C), 23.3 (CH_3), 23.0 (CH_3), 22.9 (CH_2), 20.2 (2x CH_3), 19.0 (CH_3), 18.5 (CH_3), - 2.6 (CH_3), - 3.2 (CH_3).

MS (FAB) *m/z* = 422 $(M+H)^+$.

HRMS: 422.3056, ($C_{24}H_{43}O_3NSi$+H) requires, 422.3090.



190 **191**

(2a*S*,5*R*,5a*S*,8*S*,8a*R*,8b*S*)-8b-(2-Acetamidoethyl)-5-methyl-2a,5,5a,6,7,8,8a,8b-octahydro-2H-benzo[cd]isobenzofuran-8-ol (191):

To a solution of tricycle **190** (90 mg, 0.21 mmol) in acetonitrile (9.5 mL) was added 45% aqueous HF (0.5 mL). The mixture was stirred at rt for 1.5 h and another portion of 45% aqueous HF (0.5 mL) was added. After stirring an additional 2 h, the mixture was neutralized with a 10% NaOH solution and extracted with diethyl ether (3x 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by column chromatography (95:5 ethyl acetate/methanol) to obtain the alcohol **191** (24 mg, 65%) as a colorless, viscous oil. Crystallization from d-chloroform (the solution was allowed to evaporate slowly from a capped tube at rt over 5-6

weeks) afforded single crystals suitable for X-ray analysis; mp 186-188° C; R_f = 0.21 (95:5 ethyl acetate/methanol); $[\alpha]_D^{29}$ + 5.75 (c = 0.40, $CHCl_3$).

Found: C, 68.59; H, 8.98; N, 5.03. ($C_{16}H_{25}NO_3$) requires: C, 68.79; H, 9.02; N, 5.01%.

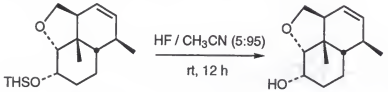
IR (neat) ν = 3680, 3020, 2980, 1730, 1670, 1520, 1420, 1210, 1050 cm^{-1}.

^1H NMR: δ = 5.60 (bs, 1H), 5.49 (bs, 1H), 4.15 (t, J = 8.3 Hz, 1H), 3.94 (m, 1H), 3.85 (d, J = 5.6 Hz, 1H), 3.63 (dd, J = 12.0, 7.6, Hz, 1H), 3.41 (m, 1H), 3.18 (m, 2H), 2.21 (bs, 1H), 1.94 (s, 3H), 1.90 (bs, 1H), 1.68 (m, 3H), 1.43 (m, 1H), 1.26 (m, 3H), 1.15 (d, J = 7.8 Hz, 3H).

^{13}C NMR: δ = 170.0 (C), 135.5 (CH), 122.0 (CH), 80.2 (CH), 69.2 (C), 66.5 (CH), 45.5 (C), 42.4 (CH), 40.6 (CH), 37.4 (CH), 35.8 (CH_2), 31.2 (CH_2), 28.3 (CH_2), 23.3 (CH_3), 22.9 (CH_3), 22.6 (CH_2).

MS (CI/methane): *m/z* = 280 ($M+H^+$, 100%), 262 (35).

HRMS: 280.1959, ($C_{16}H_{25}NO_3$+H) requires, 280.1912.



195 **196**

(2a*S*,5*R*,5a*S*,8*S*,8a*R*,8b*S*)-5,8b-Dimethyl-2a,5,5a,6,7,8,8a,8b-octahydro-2H-benzoisobenzofuran-8-ol (196):

To a solution of tricyclic silyl ether **195** (74 mg, 0.24 mmol) in acetonitrile (9.5 mL) was added 48% aqueous HF (0.5 mL). The reaction mixture was stirred at rt for 12 h. Water (40 mL) was added, the aqueous phase was neutralized with a 10% NaOH solution and extracted with diethyl ether (3x 25 mL). The combined organic phases were washed with brine and dried ($MgSO_4$). After concentration by rotary evaporation, the crude product was purified by flash column chromatography (4:1 hexanes/ethyl acetate) to afford the tricyclic

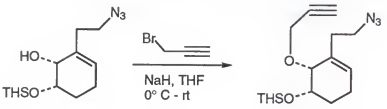
alcohol **196** (32 mg, 73%) as a colorless, viscous oil which crystallized from $CDCl_3$ by slow evaporation to obtain single crystals for X-ray analysis; R_f = 0.20 (4:1 hexanes/ethyl acetate).

IR ($CHCl_3$): ν = 3420, 3020, 2960, 2930, 2870, 1210 cm^{-1}.

^1H NMR: δ = 5.63 (dt, J= 9.5, 2.2 Hz, 1H), 5.56 (dt, J = 9.5, 2.2 Hz, 1H), 4.12 (t, J = 7.6 Hz, 1H), 3.90 (m, 1H), 3.64 (m, 2H), 3.02 (m, 1H), 2.51 (s, 1H), 1.90 (m, 2H), 1.62 (m, 1H), 1.38 (m, 3H), 1.12 (d, J = 7.6 Hz, 3H), 0.88 (s, 3H).

^{13}C NMR: δ = 135.0 (CH), 122.3 (CH), 84.2 (CH), 69.6 (CH_2), 66.4 (CH), 47.7 (CH), 42.9 (CH_2), 39.6 (CH_3), 37.3 (CH_3), 28.5 (CH_2), 23.2 (CH), 23.0 (CH), 22.7 (CH_2).

HRMS: 209.1504 ($C_{13}H_{20}O_2$+H) requires 209.1541.



186 **222**

(5*S*,6*R*)-1-(2-Azidoethyl)-6-(1-propynyloxy)-5-(thexyldimethylsiloxy)-)1-cyclohexene (222):

To a precooled (0° C) solution of NaH (40 mg, 1.0 mmol, 60% suspension in mineral oil) in THF (4 mL) was added dropwise a solution of azide **186** (218 mg, 0.67 mmol) in THF (4 mL). The reaction mixture was stirred for 35 min. and then propargyl bromide (95 mg, 90 μL, 0.80 mmol) was added dropwise. The cooling bath was removed and the mixture stirred for 48 h. Water (25 mL) was added and the crude product was extracted into diethyl ether(5x 25 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by column chromatography (9:1 hexanes/ethyl acetate) to afford alkyne **222** (175 mg, 72%) as a colorless oil; R_f = 0.63 (9:1 hexanes/ethyl acetate); $[\alpha]_D^{28}$

- 32.8 (c = 0.96, $CHCl_3$).

Found: C, 62.85; H, 9.24; N, 11.46. ($C_{19}H_{33}N_3O_2Si$) requires: C, 62.77; H, 9.15; N, 11.56%.

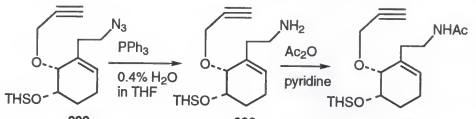
IR ($CHCl_3$): ν = 2960, 2870, 2100, 1630, 1460, 1380, 1250, 1090, 1070 cm^{-1}.

^1H NMR: δ = 5.61 (bs, 1H), 4.50 (dd, J = 16.0, 2.4 Hz, 2H), 3.91 (d, J = 3.0 Hz, 1H), 3.84 (dt, J = 11.3, 3.3 Hz, 1H), 3.40 (m, 2H), 2.48 (m, 1H), 2.44 (t, J = 2.4 Hz, 1H), 2.38 (m, 1H), 2.19 (m, 1H), 2.03 (m, 1H), 1.90 (m, 1H), 1.65 (p, J = 6.9 Hz, 1H), 1.57 (m, 1H), 0.91 (s, 3H), 0.88 (s, 3H), 0.85 (s, 6H), 0.13 (s, 6H).

^{13}C NMR: δ = 133.0 (C), 128.3 (CH), 81.1 (C), 75.5 (CH), 74.4 (CH_2), 72.5 (CH), 59.2 (CH_2), 50.3 (CH_2), 34.1 (CH_2), 34.0 (CH_3), 25.5 (CH_2), 25.1 (CH_2), 25.0 (C), 20.4 (CH_3), 20.2 (CH_3), 18.6 (CH_3), 18.5 (CH_3), - 2.5 (CH_3), - 2.6 (CH_3).

MS (CI/methane): *m/z* = 364 ($M+H^+$, 25%), 321 (55), 280 (45), 237 (50), 194 (20), 120 (100).

HRMS: 364.2416, ($C_{19}H_{33}N_3O_2Si+H$) requires, 364.2420.



222 **223** **224**

(5*S*,6*R*)-1-(2-Acetimidoethyl)-6-(1-propynyloxy)-5-(thexyldimethylsiloxy)-1-cyclohexene (224):

To a solution of azide **222** (264 mg, 0.73 mmol) in THF (16 mL) was added PPh_3 (286 mg, 1.09 mmol) followed by water (0.064 mL). The mixture was heated at reflux for 16 h and was then concentrated under reduced pressure. Water (25 mL) was added and the crude product was extracted into diethyl ether (1x 15 mL). The organic phase was washed

with 10% citric acid (3x 15 mL) to remove the crude amine. After adjusting the aqueous phase to pH = 12 with 10% NaOH, the crude amine was extracted into diethyl ether (3x 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to afford amine **223** (246 mg) which was taken directly to the protection reaction. To a solution of crude amine **223** (246 mg, 0.73 mmol) in pyridine (4 mL) was added acetic anhydride (448 mg, 414 µL, 2.19 mmol). The reaction mixture was stirred at rt for 30 min. After concentration under high vacuum, the crude product was purified by column chromatography (ethyl acetate) to afford acetamide **224** (184 mg, 66% overall from azide **222**) as a pale yellow oil; $R_f = 0.50$ (ethyl acetate); $[\alpha]_D^{28}$ - 70.1 (c = 1.21, $CHCl_3$).

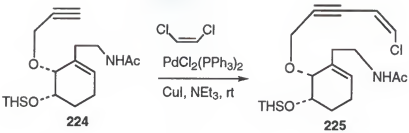
IR ($CHCl_3$): ν = 3020, 2980, 1650, 1520, 1420, 1230, 1200, 1050 cm^{-1}.

^1H NMR: δ = 6.01 (bs, 1H), 5.54 (bs, 1H), 4.49 (d, J = 2.4 Hz, 2H), 3.81 (m, 2H), 3.37 (q, J = 6.4 Hz, 2H), 2.44 (t, J = 2.2 Hz, 1H), 2.37 (m, 1H), 2.21-2.00 (m, 3H), 1.94 (s, 3H), 1.63 (p, J = 6.8 Hz, 1H), 1.57 (m, 1H), 0.89 (d, J = 1.2 Hz, 3H), 0.87 (d, J = 1.2 Hz, 3H), 0.84 (d, J = 1.2 Hz, 6H), 0.12 (s, 6H).

^{13}C NMR: δ = 170.0 (C), 133.5 (C), 128.0 (CH), 80.6 (C), 76.7 (CH), 74.5 (CH_2), 72.6 (CH), 59.2 (CH_2), 38.5 (CH_2), 34.4 (CH_2), 34.0 (CH_3), 25.4 (CH_2), 24.9 (CH_2), 24.8 (C), 23.3 (CH), 20.2 (CH_3), 20.1 (CH_3), 18.6 (CH_3), 18.5 (CH_3), - 2.7 (CH_3).

MS (FAB): *m/z* = 380 ($M+H^+$, 15%), 324 (100), 265 (85), 235 (50), 164 (15), 136 (25).

HRMS: 380.2619, ($C_{21}H_{37}NO_3Si+H$) requires, 380.2621.



(5*S*,6*R*)-(1*Z*)-1-(2-Acetimidoethyl)-6-(1-chloro-1-penten-3-ynoxy)-5-(thexyldimethylsiloxy)-1-cyclohexene (225):

To a solution of $PdCl_2(PPh_3)_2$ (13.6 mg, 0.02 mmol) and CuI (0.9 mg, 0.01 mmol) in dry triethylamine (1 mL) was added *cis*-dichloroethylene (94 mg, 74 μL, 0.97 mmol). The suspension was stirred for 5 min., and the solution changed to a bright yellow. To the mixture was added dropwise a solution of alkyne **224** (37 mg, 0.10 mmol) in triethylamine (1 mL) in 4 portions at 15 min. intervals. A brown precipitate was observed after the final addition and the mixture turned dark brown. After 30 min. of stirring, the mixture was concentrated under reduced pressure, and the crude product was purified by column chromatography (ethyl acetate) to afford enyne **225** (8 mg, 19%) as a brown oil; R_f = 0.51 (ethyl acetate); $[\alpha]_D^{27}$ - 53.7 (c = 0.86, $CHCl_3$).

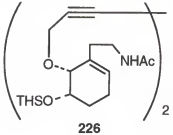
IR (neat): ν = 3300, 2950, 2860, 1650, 1550, 1440, 1380, 1250, 1120, 1090, 1060, 830 cm^{-1}.

^1H NMR: δ = 6.40 (d, J = 7.3 Hz, 1H), 5.98 (bs, 1H), 5.92 (dt, J = 7.6, 2.0 Hz, 1H), 5.56 (bs, 1H), 4.71 (dd, J = 16.6, 2.0 Hz, 2H), 3.92 (bs, 1H), 3.84 (dt, J = 9.1, 3.1 Hz, 1H), 3.38 (q, J = 6.0 Hz, 2H), 2.38 (m, 1H), 2.18 (m, 2H), 2.05 (m, 1H), 1.94 (s, 3H), 1.89 (m, 1H), 1.65 (p, J = 6.9 Hz, 1H), 1.63 (m, 1H), 0.91 (s, 3H), 0.89 (s, 3H), 0.86 (s, 6H), 0.14 (s, 6H).

^{13}C NMR: δ = 170.2, 133.6, 128.8, 128.2, 111.6, 94.5, 80.3, 72.6, 59.8, 38.7, 34.4, 34.0, 25.4, 25.0, 24.9, 23.2, 20.3, 20.3, 18.6, 18.5, - 2.6.

MS (FAB): *m/z* = 440 ($M+H^+$, 75%), 324 (80), 265 (100).

HRMS: 440.2388, ($C_{23}H_{38}NO_3Si+H$) requires, 440.2387.



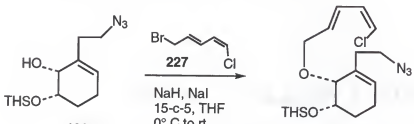
226

The major product was dimerized starting acetamide **226** (21 mg, 70%) isolated as a dark brown oil; R_f = 0.28 (ethyl acetate).

^1H NMR (300 MHz, $CDCl_3$): δ = 6.27 (bs, 1H), 5.55 (bs, 1H), 4.58 (s, 2H), 3.80 (m, 2H), 3.36 (q, J = 6.4 Hz, 2H), 2.35 (m, 1H), 2.18 (m, 2H), 1.95 (s, 3H), 1.86 (m, 2H), 1.62 (m, 2H), 0.89 (s, 3H), 0.87 (s, 3H), 0.84 (s, 6H), 0.12 (s, 6H).

MS (FAB): *m/z* = 757 ($M+H^+$, 5%), 265 (100).

HRMS: 757.5015, ($C_{42}H_{72}N_2O_6Si_2+H$) requires, 757.5007.



186 **228**

(5*S*,6*R*)-(1*Z*,3*E*)-1-(2-Azidoethyl)-6-(1-chloro-1,3-pentadienyloxy)-5-(thexyldimethysiloxy)-1-cyclohexene (228):

To a precooled (0° C) solution of the azide **186** (1.14 g, 3.50 mmol) in THF (15 mL) was added NaH (280 mg, 7.00 mmol, 60% suspension in mineral oil). The reaction mixture was stirred at 0° C for 45 min. A solution of bromodiene **227** (953 mg, 5.35 mmol) in THF (15 mL) was added dropwise, followed by NaI (524 mg, 3.50 mmol) and 2 drops of 15-c-5 crown ether. The cooling bath was removed and the reaction mixture stirred for 37.5 h. Water (50 mL) was added and the crude product was extracted into Et_2O (4x 25

mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by column chromatography (95:5 hexanes/ethyl acetate) to afford ether **228** (841 mg, 56% isolated) as a dark yellow oil. [Note: Some unreacted starting azide (242 mg) was also isolated, and the recalculated yield based on the recovery was 72%]; R_f = 0.27 (95:5 hexanes/ethyl acetate); $[\alpha]_D^{28}$ - 64.4 (c = 1.55, $CHCl_3$).

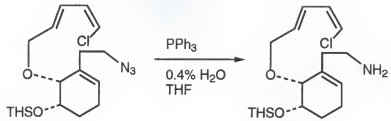
IR ($CHCl_3$): ν = 2960, 2870, 2100, 1720, 1680, 1460, 1250, 1090, 830 cm^{-1}.

^1H NMR: δ = 6.65 (dd, J = 14.6, 10.4 Hz, 1H), 6.32 (dd, J = 10.4, 7.2 Hz, 1 H), 6.02 (d, J = 7.2 Hz, 1H), 5.96 (m, 1H), 5.58 (bs, 1H), 4.56 (dd, J = 12.9, 5.2 Hz, 1H), 4.19 (dd, J = 12.9, 6.9, 1H), 3.85 (dt, J = 11.0, 3.0, 1H), 3.68 (d, J = 3.0 Hz, 1H), 3.35 (m, 2H), 2.36 (t, J = 6.3, 2H), 2.20 (m, 1H), 2.02 (m, 1H), 1.94 (m, 1H), 1.68 (p, J = 6.9 Hz, 1H), 1.60 (m, 1H), 0.92 (s, 3H), 0.89 (s, 3H), 0.87 (s, 6H), 0.14 (s, 6H).

^{13}C NMR: δ = 134.2 (CH), 133.3 (C), 129.2 (CH), 127.5 (CH), 125.4 (CH), 118.5 (CH), 77.7 (CH), 72.6 (CH_2), 71.9 (CH), 50.3 (CH_2), 34.2 (CH_2), 34.1 (CH), 25.7 (CH_2), 24.9 (C), 24.8 (CH_2), 20.3 (CH_3), 20.2 (CH_3), 18.6 (CH_3), 18.5(CH_3), - 2.5 (CH_3), - 2.6 (CH_3).

MS (FAB): *m/z* = 426 ($M+H^+$, 40%) 308 (35), 280 (65), 154 (100).

HRMS: 426.2348, ($C_{21}H_{36}N_3O_2SiCl+H$) requires, 426.2343.



228 **229**

(5*S*,6*R*)-(1*Z*,3*E*)-1-(2-Aminoethyl)-6-(1-chloro-1,3-pentadienyloxy)-5-(thexyldimethysiloxy)-1-cyclohexene (229):

To a solution of the azide **228** (228 mg, 0.54 mmol) in THF (16 mL) was added PPh_3 (210 mg, 0.80 mmol) followed by water (64 μL). The mixture was heated at reflux for 18 h. After removal of the solvent under reduced pressure, the crude product was purified by flash column chromatography (ethyl acetate saturated with ammonium hydroxide) to afford an oily product combined with silica gel residue. The oil was dissolved into hexanes and separated from the solid by filtration. Removal of the hexanes under reduced pressure afforded the amine **229** (100 mg, 46%) as a pale yellow oil: R_f = 0.10 (ethyl acetate sat. with NH_4OH); $[\alpha]_D^{25}$ - 74.4 (c = 0.94, $CHCl_3$).

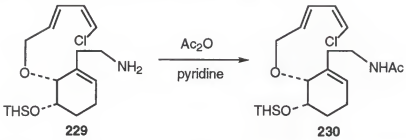
IR ($CHCl_3$): ν = 3370, 2960, 2870, 1650, 1590, 1460, 1340, 1250, 1090, 830 cm^{-1}.

^1H NMR: δ = 6.64 (dd, J = 15.1, 10.7 Hz, 1H), 6.32 (dd, J = 10.2, 7.2 Hz, 1 H), 5.98 (d, J = 6.6 Hz, 1H), 5.95 (m, 1H), 5.52 (bs, 1H), 4.58 (dd, J = 12.9, 5.5 Hz, 1H), 4.19 (dd, J = 12.6, 6.6, 1H), 3.81 (dt, J = 11.0, 3.0, 1H), 3.62 (s, 1H), 2.80 (bs, 2H), 2.20 (m, 3H), 1.99 (m, 2H), 1.80 (bs, 2H), 1.66 (p, J = 6.6 Hz, 1H), 1.58 (m, 1H), 0.92 (s, 3H), 0.89 (s, 3H), 0.86 (s, 6H), 0.13 (s, 6H).

^{13}C NMR: δ = 134.4 (CH), 134.3 (C), 129.3 (CH), 126.8 (CH), 125.2 (CH), 118.3 (CH), 78.0 (CH), 72.9 (CH_2), 72.6 (CH), 40.4 (CH_2), 39.0 (CH_2), 34.0 (CH), 25.5 (CH_2), 25.0 (C), 20.3 (CH_3), 20.2 (CH_3), 18.6 (CH_3), 18.5 (CH_3), - 2.5 (CH_3).

MS (FAB): *m/z* = 400 ($M+H^+$, 100%), 282 (50), 265 (60), 122 (65), 101 (85).

HRMS: 400.2433, ($C_{21}H_{38}NO_2SiCl$+H) requires, 400.2439.



229 **230**

(5*S*,6*R*)-(1*Z*,3*E*)-1-(2-Acetamidoethyl)-6-(1-chloro-1,3-pentadienyloxy)-5-(thexyldimethysiloxy)-1-cyclohexene (230):

To a solution of amine **229** (30 mg, 0.08 mmol) in pyridine (2 mL) was added Ac_2O (35 μL, 0.37 mmol). The mixture was stirred at rt for 16 h. After removal of the solvent under reduced pressure, the crude product was purified by column chromatography (ethyl acetate) to afford acetamide **230** (19.4 mg, 57%) as a colorless oil; R_f = 0.50 (ethyl acetate); $[\alpha]_D^{26}$ - 65.9 (c = 0.46, $CHCl_3$).

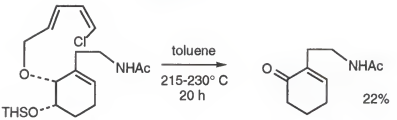
IR ($CHCl_3$): ν = 3020, 2960, 1660, 1520, 1430, 1380, 1200, 1090, 800 cm^{-1}.

^1H NMR: δ = 6.66 (dd, J = 14.6, 10.4 Hz, 1H), 6.32 (dd, J = 10.4, 7.2 Hz, 1H), 6.02 (d, J = 7.2 Hz, 1H), 5.96 (m, 1H), 5.54 (bs, 1H), 4.62 (dd, J = 12.4, 5.2 Hz, 1H), 4.18 (dd, J = 12.6, 6.6, 1H), 3.85 (dt, J = 8.0, 3.0, 1H), 3.65 (d, J = 3.0 Hz, 1H), 3.36 (m, 2H), 2.35 (m, 1H), 2.10 (m, 3H), 1.95 (m, 1H), 1.92 (s, 3H), 1.66 (m, 3H), 0.92 (s, 3H), 0.90 (s, 3H), 0.87 (s, 6H), 0.14 (s, 6H).

^{13}C NMR: δ = 170.1, 133.8, 129.1, 127.6, 125.5, 118.7, 78.4, 72.5, 72.1, 38.5, 34.6, 34.1, 25.7, 25.0, 24.8, 23.3, 20.3, 20.2, 18.6, 18.5, - 2.5.

MS (FAB): *m/z* = 442 ($M+H^+$, 50%), 324 (90), 265 (100).

HRMS: 442.2521, ($C_{23}H_{40}NO_3SiCl$+H) requires, 442.2544.



230 **232**

2-(2-Acetamidoethyl)-2-cyclohexen-1-one (232):

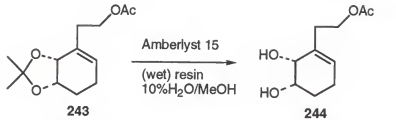
A degassed solution of triene **230** (17.6 mg, 0.04 mmol) in toluene (1 mL) was sealed under an atmosphere of argon in a glass reaction tube. The reaction tube was placed in a preheated (230° C) sand bath for 20 h. The tube was cooled to - 78° C, and carefully opened. The contents were removed and concentrated under reduced pressure. The crude product was purified by column chromatography to afford alcohol **231** (6 mg, 45%) as the major product as well as enone **232** (1.6 mg, 22%) as a yellow oil; R_f = 0.11 (ethyl acetate).

^{1}H NMR: δ = 5.87 (bs, 1H), 5.47 (bs, 1H), 3.46 (q, J = 6.4 Hz, 2H), 2.38 (m, 6 H), 2.01 (p, J = 6.4 Hz, 2H), 1.97 (s, 3H).

^{13}C NMR: δ = 127.0, 38.0, 37.2, 36.8, 29.7, 29.4, 22.6.

MS (FAB): *m/z* = 363 (2x M+H$^+$, 10%), 182 (M+H$^+$, 100), 123 (60).

HRMS: 182.1190, ($C_{10}H_{15}NO_2$+H) requires 182.1181.



243 **244**

(1*R*,2*S*)-3-(2-Acetoxyethyl)-3-cyclohexene-1,2-diol (244):

To a solution of acetonide **243** (530 mg, 2.20 mmol) in MeOH (10 mL) was added water (1 mL) followed by Amberlyst 15(wet) ion exchange resin (500 mg). The reaction mixture was stirred at rt for 7 h and then heated to 40° C over an additional 5 h. The resin was

removed by filtration and the solvent was removed under reduced pressure with benzene added to azeotrope residual water. The crude product was purified by column chromatography (7:3 ethyl acetate/hexanes) to afford diol **244** (296 mg, 67%) as a viscous yellow oil; R_f = 0.15 (1:1 ethyl acetate/hexanes); $[\alpha]_D^{26}$ - 89.6 (c = 1.36, $CHCl_3$).

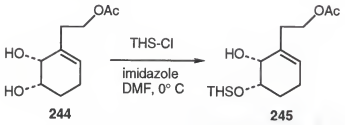
IR ($CHCl_3$): ν = 3440, 3030, 2930, 1730, 1430, 1370, 1250, 1040 cm^{-1}.

^1H NMR: δ = 5.61 (bs, 1H), 4.21 (m, 2H), 4.01 (d, J = 3.4 Hz, 1H), 3.73 (p, J = 4.5, Hz, 1H), 2.64 (s, 2H), 2.44 (m, 1H), 2.16 (m, 1H), 2.02 (s, 3H), 1.69 (m, 2H).

^{13}C NMR: δ = 171.4 (C), 133.6 (C), 128.0 (CH), 69.5(CH), 68.9 (CH), 63.4 (CH_2), 34.2(CH_2), 25.2 (CH_2), 23.9 (CH_2), 21.0 (CH_3).

MS (CI/methane): *m/z* = 201($M+H^+$, 50%), 183 (25), 141 (30), 123 (100).

HRMS: 201.1159, ($C_{10}H_{16}O_4$+H) requires, 201.1127.



244 **245**

(1*R*,6*S*)-2-(2-Acetoethyl)-6-(dimethylthexylsiloxy)-2-cyclohexene-1-ol (245):

To a precooled (0° C) solution of diol **244** (283 mg, 1.41 mmol) in dry DMF (1 mL) was added imidazole (116 mg, 1.70 mmol) followed by dimethylthexylsilyl chloride (303 mg, 333 μL, 1.70 mmol). The reaction mixture was briefly agitated and allowed to stand at 0° C for 40 h. Water (35 mL) was added and the crude product was extracted into Et_2O (4x 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by column chromatography (4:1 hexanes/ethyl acetate) to give silyl ether **245** (369 mg, 76%) as a colorless oil; R_f = 0.39 (4:1 hexanes/ethyl acetate 4:1); $[\alpha]_D^{26}$ - 35.1 (c = 1.58, $CHCl_3$).

Found: C, 63.21; H, 9.93. ($C_{18}H_{34}O_4Si$) requires: C, 63.11; H, 10.00%.

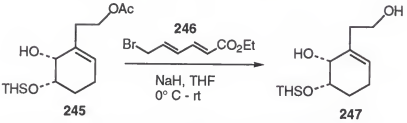
IR (neat): ν = 3550, 2960, 1740, 1470, 1370, 1250, 1090 cm^{-1}.

^1H NMR: δ = 5.59 (bs, 1H), 4.25 (dt, J = 10.7, 7.1 Hz, 1H), 4.13 (m, 1H), 3.89 (d, J = 3.9 Hz, 1H), 3.77 (dt, J = 10.7, 3.9 Hz, 1H), 2.44 (m, 3H), 2.14 (m, 1H), 2.02 (s, 3H), 1.98 (m, 1H), 1.75 (m, 1H), 1.63 (p, J = 6.8 Hz, 1H), 1.55 (m, 1H), 0.89 (d, J = 2.0 Hz, 3H), 0.87 (d, J = 1.7 Hz, 3H), 0.85 (s, 6H), 0.14 (s, 6H).

^{13}C NMR: δ = 171.0 (C), 133.6 (C), 127.0 (CH), 70.8 (CH), 68.9 (CH), 63.2 (CH_2), 34.2 (CH_3), 33.9 (CH_2), 25.3 (CH_2), 24.9 (C), 24.2 (CH_2), 21.0 (CH_3), 20.4 (CH_3), 20.2 (CH_3), 18.6 (CH_3), 18.5 (CH_3), - 2.4 (CH_3), - 3.0 (CH_3).

MS (FAB): *m/z* = 343 ($M+H^+$, 55%) 325 (60), 265 (70), 197 (100).

HRMS: 343.2317, ($C_{18}H_{34}O_4Si$+H) requires, 343.2304.

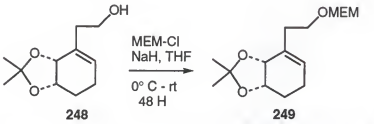


2-(2-Hydroxyethyl)-6-(dimethylthexylsiloxy)-2-cyclohexen-1-ol (247):

To a precooled (0° C) solution of NaH (14 mg, 2.09 mmol, 60% dispersion in mineral oil) in THF (2 mL) was added a solution of acetate **245** (30 mg, 0.09 mmol) in THF (1 mL). The reaction mixture was stirred for 25 min. A solution of ethyl 6-bromocrotonate **246** (23 mg, 0.11 mmol) in THF (1 mL) was added dropwise, the cooling bath was removed, and the reaction mixture was stirred for 14 h. Water (15 mL) was added and the crude product was extracted into EtOAc (3x 15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by column chromatography to give diol **247** (20 mg, 77%) as a colorless oil; R_f = 0.43 (1:1 hexanes/ethyl acetate).

^{1}H NMR: δ = 5.62 (bs, 1H), 3.88 (d, J = 3.4 Hz, 1H), 3.79 (m, 2H), 3.64 (m, 1H), 2.68 (bs, 2H), 2.44 (m, 1H), 2.27 (m, 1H), 2.11 (m, 2H), 1.77 (m, 1H), 1.64 (p, J = 6.8 Hz, 1H), 1.56 (m, 1H), 0.91 (s, 3H), 0.89 (s, 3H), 0.86 (s, 6H), 0.14 (s, 3H), 0.13 (s, 3H).

^{13}C NMR: δ = 134.9 (C), 128.6 (CH), 71.0 (CH), 69.3 (CH), 62.3 (CH_2), 40.1 (CH_2), 34.2 (CH), 24.8 (CH_2), 24.7 (CH_2), 21.5 (C), 20.3 (CH_3), 20.2 (CH_3), 18.6 (CH_3), 18.5 (CH_3), - 2.4 (CH_3), - 2.9 (CH_3).



248 **249**

(3a*S*,7a*R*)-2,2-Dimethyl-7-(2-(2-methoxyethyloxymethyloxy)ethyl)-4,5-dihydrobenzo[d][1,3]dioxole (249):

To a precooled (0° C) flask containing NaH (203 mg, 5.09 mmol, 60% suspension in mineral oil) was added dropwise a solution of alcohol **248** (673 mg, 3.39 mmol) in THF (15 mL). The reaction mixture was stirred for 30 min., gas evolution was observed, and MEM-Cl (507 mg, 465 μL, 4.07 mmol) was added dropwise. The cooling bath was removed and the reaction stirred for 48 h. Water (100 mL) was added and the product was extracted into diethyl ether (5x 25 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by column chromatography (1:1 hexanes/ethyl acetate) to afford ether **249** (796 mg, 82%) as a pale yellow oil; R_f = 0.52 (1:1 ethyl acetate/hexanes); $[\alpha]_D^{27}$ + 14.9 (c = 1.64, $CHCl_3$).

Found: C, 62.76; H, 9.22. ($C_{15}H_{26}O_5$) requires: C, 62.91; H, 9.15%.

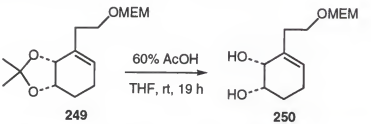
IR ($CHCl_3$): ν = 3010, 2930, 2890, 1460, 1380, 1370, 1240, 1040 cm $^{-1}$.

^{1}H NMR: δ = 5.65 (bs, 1H), 4.78 (d, J = 6.9 Hz, 1H), 4.71 (s, 1H), 4.36 (d, J = 5.2 Hz, 1H), 4.28 (m, 1H), 3.69 (m, 4H), 3.54 (m, 2H), 3.38 (s, 3H), 2.39 (m, 2H), 2.14 (m, 1H), 1.92 (m, 1H), 1.84 (m, 1H), 1.73 (m, 1H), 1.37 (s, 6H).

^{13}C NMR: δ = 133.1 (C), 126.5 (CH), 108.3 (C), 95.4 (CH_2), 92.0 (CH_2), 73.8 (CH),73.4 (CH), 71.8 (CH_2), 66.7 (CH_2), 66.1 (CH_2), 58.9 (CH_3), 34.0 (CH_2), 27.9 (CH_3), 26.5 (CH_3), 25.4 (CH_2), 20.8 (CH_2).

MS (FAB): *m/z* = 287 ($M+H^+$, 10%) 211 (50),153 (55), 123 (100), 89 (75).

HRMS: 287.1863, ($C_{15}H_{26}O_5$+H) requires, 287.1858.



249 **250**

(1*S*,2*R*)-3-[2-(2-Methoxyethyloxymethyloxy)ethyl]-3-cyclhexene-1,2-diol (250):

To a solution of acetonide **249** (347 mg, 1.21 mmol) in THF (2 mL) was added 60% AcOH (2 mL). The reaction mixture was stirred at rt for 19 h and concentrated AcOH (1 mL) was added. After an additional 3 h stirring, water (20 mL) was added and the mixture was neutralized with 10% KOH. The crude product was extracted into ethyl acetate (10x 20 mL) and purified by column chromatography (ethyl acetate) to afford diol **250** (257 mg, 85%) as a colorless oil; R_f = 0.18 (7:3 ethyl acetate/hexanes); $[\alpha]_D^{27}$ - 63.6 (c = 1.31, $CHCl_3$).

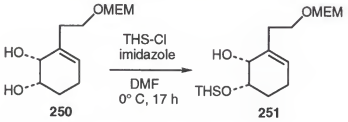
IR (neat): ν = 3420, 2930, 1730, 1650, 1450, 1400, 1240, 1200, 1110 cm^{-1}.

^{1}H NMR: δ = 5.61 (bs, 1H), 4.78 (s, 1H), 4.72 (s, 1H), 3.97 (d, J = 3.8 Hz, 1H), 3.75-3.64 (m, 5H), 3.54 (m, 2H), 3.37 (s, 3H), 2.90 (bs, 2H), 2.42 (m, 1H), 2.33 (m, 1H), 2.13 (m, 1H), 2.05 (m, 1H), 1.69 (m, 2H).

^{13}C NMR: δ = 135.3, 127.4, 95.4, 71.7, 69.5, 68.8, 68.7, 67.6, 67.0, 35.2, 25.4, 24.0.

MS (FAB): *m/z* = 247 (M+H$^+$, 100%).

HRMS: 247.1549, ($C_{12}H_{22}O_5$+H) requires, 247.1545.



250 **251**

(1*S*,2*R*)-3-[2-(2-Methoxyethyloxymethyloxy)ethyl]-6-(thexyldimethylsiloxy)-2-cyclhexene-1-ol (251):

To a precooled (0° C) solution of diol **250** (115 mg, 0.47 mmol) in DMF (1 mL) was added imidazole (35 mg, 0.51 mmol) followed by THS-Cl (92 mg, 0.51 mmol). The mixture was agitated briefly then allowed to stand at 0° C for 17 h. Water (25 mL) was added and the crude product was extracted into diethyl ether (5x 20 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by column chromatography (7:3 hexanes/ethyl acetate) to afford silyl ether **251** (145 mg, 80%) as a colorless oil; R_f = 0.33 (7:3 hexanes/ethyl acetate), $[\alpha]_D^{26}$ -29.3 (c = 1.42, $CHCl_3$).

IR ($CHCl_3$): ν = 3550, 2950, 2880, 1470, 1380, 1250, 1080 cm^{-1}.

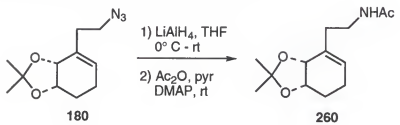
^{1}H NMR: δ = 5.60 (bs, 1H), 4.79 (d, J = 6.6 Hz, 1H), 4.72 (s, 1H), 3.88 (bs, 1H), 3.78 (dt, J = 11.0, 3.6 Hz, 1H), 3.68 (m, 4H), 3.55 (m, 2H), 3.38 (d, 2H), 2.67 (bs, 1H), 2.41 (d, J = 4.7 Hz, 2H), 2.15 (m, 1H), 2.0 (m, 1H), 1.76 (m, 1H), 1.64 (p, J = 6.9 Hz,

1H), 1.54 (m, 1H), 0.90 (d, J = 1.7 Hz, 3H), 0.88 (d, J = 1.7 Hz, 3H), 0.85 (s, 6H), 0.13 (d, J = 1.7 Hz, 6H).

^{13}C NMR: δ = 134.6 (CH), 126.3 (CH), 95.4 (CH_2), 71.8 (CH_2), 71.0 (CH), 69.0 (CH), 67.2 (CH_2), 34.9 (CH_2), 34.2 (CH), 25.3 (CH_2), 24.9 (C), 24.2 (CH_2), 20.4 (CH_3), 20.2 (CH_3), 18.6 (CH_3), 18.3 (CH_3), - 2.9 (CH_3).

MS (FAB): *m/z* = 389 ($M+H^+$, 15%), 371 (100), 313 (30), 197 (20), 89 (15).

HRMS: 389.2726, ($C_{20}H_{40}O_5Si$+H) requires, 389.2723.



180 **260**

(3a*S*,7a*R*)-2,2-Dimethyl-7-(2-acetamidoethyl)-4,5-dihydrobenzo[d][1,3]dioxole (260):

To a precooled (0° C) solution of azide **180** (150 mg, 0.67 mmol) in THF (30 mL) was added $LiAlH_4$ (26.7 mg, 0.67 mmol, 95% powder). The reaction mixture was stirred at 0° C for 1 h. The cooling bath was removed and the mixture stirred an additional 2 h. The reaction mixture was quenched with water (1 mL) followed by 10% NaOH (2 mL) and finally water (2 mL). The resulting gray residue was removed by filtration, and the filtrate was concentrated under reduced pressure. Benzene was added to remove residual water.

The crude amine was dissolved in pyridine (5 mL) and Ac_2O (75 mg, 70 μL, 0.74 mmol) was added dropwise. The reaction mixture was stirred at rt for 1 h and then concentrated under reduced pressure. The crude product was extracted with CH_2Cl_2 (3x 25 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by

column chromatography (5% methanol/ethyl acetate) to afford acetamide **260** (116 mg, 73%) as a pale yellow oil; R_f = 0.41 (5% methanol/ethyl acetate).

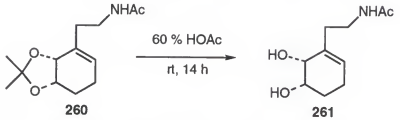
IR ($CHCl_3$): ν = 3300, 2980, 2930, 1650, 1560, 1380, 1240, 1220, 1080, 1040 cm^{-1}.

^1H NMR: δ = 6.00 (bs, 1H), 5.69 (t, J = 3.9 Hz, 1H), 4.34 (d, J = 5.6 Hz, 1H), 4.28 (ddd, J = 3.6, 5.8, 9.6 Hz, 1H), 3.39 (m, 2H), 2.41 (m, 1H), 2.17 (m, 2H), 1.95 (s, 3H), 1.75 (m, 1H), 1.64 (m, 1H), 1.40 (s, 3H), 1.38 (s, 3H).

^{13}C NMR: δ = 169.9 (C), 133.2 (C), 128.3 (CH), 108.2 (C), 73.7 (CH), 73.5 (CH), 38.3 (CH_2), 34.4 (CH_2), 27.9 (CH_3), 26.2 (CH_3), 25.7 (CH_2), 23.3 (CH_3), 21.0 (CH_2).

MS (EI): *m/z* = 240 ($M+H^+$, 55%), 182 (100), 123 (20).

HRMS: 240.1605, ($C_{13}H_{21}NO_3$+H) requires, 240.1600.



260 **261**

(1*S*,2*R*)-3-(2-Azidoethyl)-3-cyclohexene-1,2-diol (261):

To acetonide **260** (705 mg, 2.95 mmol) was added 60% acetic acid (15 mL). The reaction mixture was stirred at rt for 14 h. The acetic acid was removed under reduced pressure with the assistance of hexanes and benzene. The crude product was purified by column chromatography (4:1 ethyl acetate/methanol) to give diol **261** (397 mg, 68%) as a clear oil. The oil was crystallized from ethyl acetate and hexanes; mp 90-91° C; R_f = 0.10 (95:5 ethyl acetate/methanol); $[\alpha]_D^{26}$ - 108.0 (c = 1.0, $CHCl_3$).

Found: C, 60.18; H, 8.62; N, 7.03. ($C_{10}H_{17}NO_3$) requires: C, 60.28; H, 8.60; N, 7.03%.

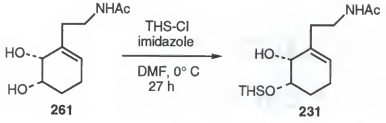
IR ($CHCl_3$): ν = 3300, 2930, 1640, 1560, 1440, 1370, 1300, 1080, 1050, 990 cm^{-1}.

^{1}H NMR: δ = 6.78 (bs, 1H), 5.53 (s, 1H), 3.95 (d, J = 3.7 Hz, 1H), 3.91 (s, 2H), 3.66 (p, J = 4.6 Hz, 1H), 3.50 (ddd, J = 13.7, 6.2 Hz, 1H), 3.21 (ddd, J = 11.7, 6.0 Hz, 1H), 2.29 (ddd, J = 14.0, 6.6 Hz, 1H), 2.19 (dt, J = 14.6, 6.0 Hz, 1H), 2.04 (m, 1H), 1.92 (s, 3H), 1.65 (m, 2H).

^{13}C NMR: δ = 171.0 (C), 134.2 (C), 128.0 (CH), 69.6 (CH), 69.1 (CH), 38.9 (CH_2), 35.9 (CH_2), 24.9 (CH_2), 24.3 (CH_2), 23.1 (CH_3).

MS (CI/methane): *m/z* = 200 ($M+H^+$, 65%), 182 (40), 164 (15).

HRMS: 200.1298, ($C_{10}H_{17}NO_3$+H) requires, 200.1287.



(1*S*,6*R*)-2-(2-Acetamidoethyl)-6-(dimethylthexylsiloxy)-2-cyclohexen-1-ol (231):

To a precooled (0° C) solution of diol **261** (285 mg, 1.43 mmol) in dry DMF (1 mL) was added imidazole (117 mg, 1.72 mmol) followed by dropwise addition of THS-Cl (308 mg, 338 μL, 1.72 mmol). The reaction mixture was agitated briefly and allowed to stand at 0° C for 27 h. Water (40 mL) was added and the crude product was extracted into Et_2O (5x 10 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was purified by column chromatography (7:3 ethyl acetate/hexanes) to afford silyl ether **231** (396 mg, 81%) as a pale yellow oil; R_f = 0.38 (7:3 ethyl acetate/hexane); $[\alpha]_D^{28}$ - 67.6 (c = 1.0, $CHCl_3$).

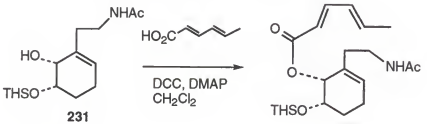
Found: C, 63.30; H, 10.33; N, 4.10. ($C_{18}H_{35}NO_3Si$) requires: C, 63.29; H, 10.36; N, 4.05 %.

IR ($CHCl_3$): ν = 3540, 3450, 3020, 2960, 2870, 1660, 1520, 1220, 1090 cm^{-1}.

^1H NMR: δ = 6.46 (bs, 1H), 5.60 (bs, 1H), 3.83 (d, J = 3.6 Hz, 1H), 3.73 (dt, J = 11.0, 3.6 Hz, 1H), 3.39 (m, 1H), 3.31 (m, 1H), 2.68 (bs, 1H), 2.39 (m, 1H), 2.12 (m, 3H), 1.94 (s, 3H), 1.73 (m, 1H), 1.63 (p, J = 6.8 Hz, 1H), 1.55 (m, 1H), 0.89 (d, J = 2.0 Hz, 3H), 0.87 (d, J = 2.0 Hz, 3H), 0.85 (s, 6H), 0.13 (s, 3H), 0.12 (s, 3H).

^{13}C NMR: δ = 170.0 (C), 134.6 (C), 127.9 (CH), 71.0 (CH), 69.3 (CH), 38.9 (CH_2), 35.4 (CH_2), 34.2 (CH_3), 24.9 (CH_2), 24.5 (CH_2), 23.2 (CH), 20.3 (CH_3), 20.1 (CH_3), 18.6 (CH_3), 18.5 (CH_3), - 2.4 (CH_3), - 3.0 (CH_3).

MS (CI/methane): *m/z* = 342 ($M+H^+$, 75%), 324 (90), 197 (25), 143 (55), 83 (100). HRMS: 342.2462, ($C_{18}H_{35}NO_3Si$+H) requires, 342.2464.



231 **262**

(5*S*,6*R*)-(2*E*,4*E*)-1-(2-Acetamidoethyl)-5-(thexyldimethylsiloxy)-6-(2,4-hexadienoic) ester (262):

To a solution of DCC (371 mg, 1.80 mmol), sorbic acid (120 mg, 1.07 mmol), and a catalytic amount of DMAP in CH_2Cl_2 (5 mL) was added a solution of alcohol **231** (123 mg, 0.36 mmol), in CH_2Cl_2 (3 mL). The reaction mixture was stirred at rt for 22 h. An additional portion of sorbic acid (100 mg), DCC (200 mg) and catalytic DMAP were added to drive the reaction toward completion and the mixture was stirred another 72 h. The mixture was filtered through celite and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (7:3 ethyl acetate/hexanes) to afford the product mixed with dicyclohexyl urea. After dissolving in hexanes, the product

was separated by filtration and following concentration under reduced pressure afforded ester **262** (54 mg, 34%) as a yellow oil; $R_f = 0.23$ (1:1 ethyl acetate/hexanes); $[\alpha]_D^{26}$ - 63.1 (c = 1.21, $CHCl_3$).

IR ($CHCl_3$): ν = 3680, 3620, 2980, 1700, 1660, 1520, 1420, 1200, 1050 cm^{-1}.

^1H NMR: δ = 6.18 (m, 2H), 5.80 (d, J = 15.4 Hz, 1H), 5.69 (bs, 1H), 5.42 (d, J = 3.6 Hz, 1H), 3.89 (dt, J = 10.2, 3.3 Hz, 1H), 3.28 (m, 1H), 2.30-2.15 (m, 3H), 2.12-2.00 (m, 2H), 1.96 (s, 3H), 1.89 (m, 1H), 1.86, (d, J = 5.5 Hz, 3H), 1.78 (m, 1H), 1.72-1.64 (m, 2H), 1.57 (p, J = 6.9 Hz, 1H), 0.85 (s, 3H), 0.83 (s, 3H), 0.78 (s, 6H), 0.09 (s, 3H), 0.06 (s, 3H).

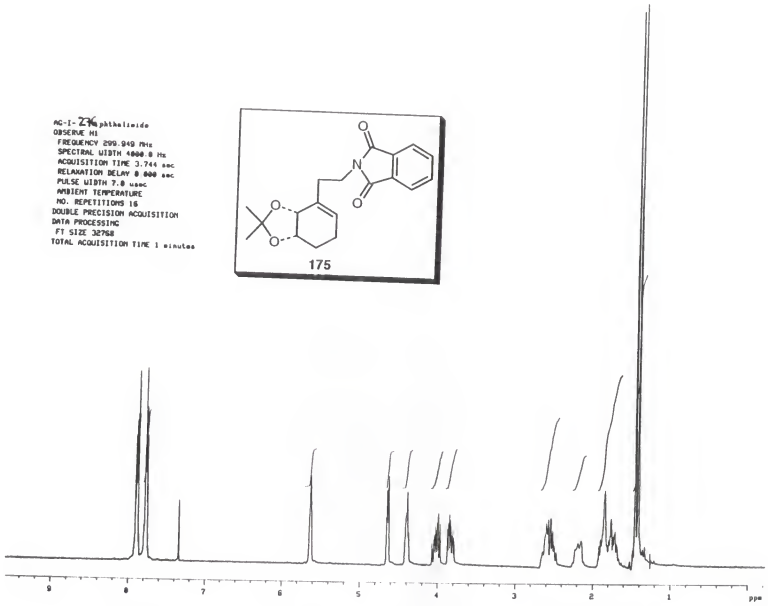
^{13}C NMR: δ = 169.9, 167.4, 145.3, 139.3, 132.2, 129.8, 128.9, 119.0, 70.8, 68.9, 38.3, 34.2, 33.8, 26.6, 25.5, 24.8, 24.0, 23.3, 20.2, 18.6, - 2.8, - 2.9.

MS (FAB): *m/z* = 436 ($M+H^+$, 20%), 324 (100), 265 (55), 95 (40).

HRMS: 436.2884, ($C_{24}H_{41}NO_4Si+H$) requires, 436.2883.

APPENDIX A
SPECTRAL DATA

The ^{1}H and ^{13}C or APT NMR spectra of selected compounds reported in Chapter 5 are graphically displayed in this appendix. The spectra along with the proposed structure are shown.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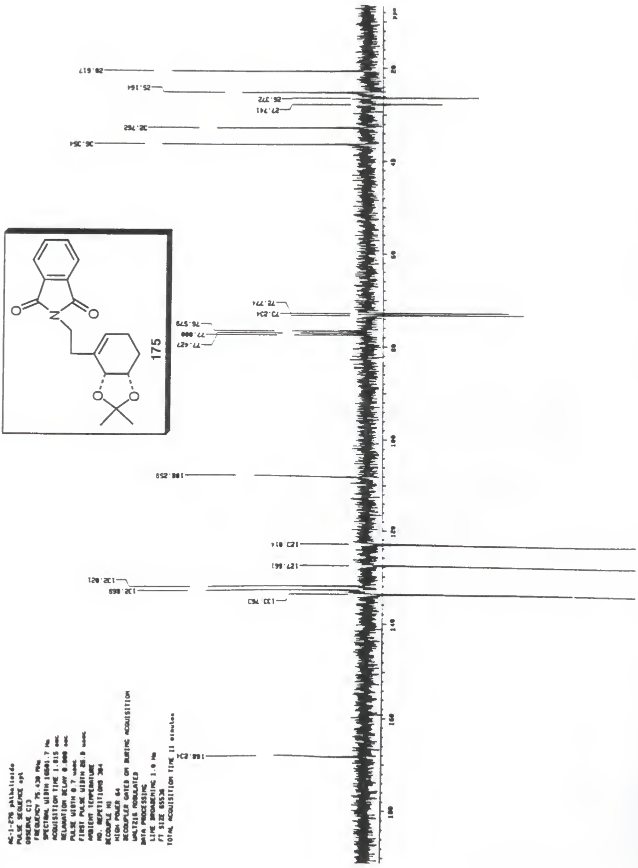
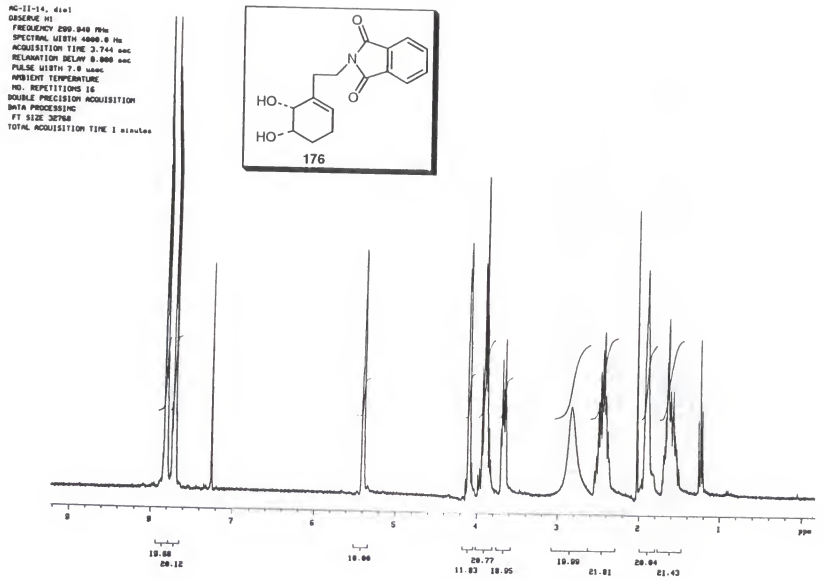
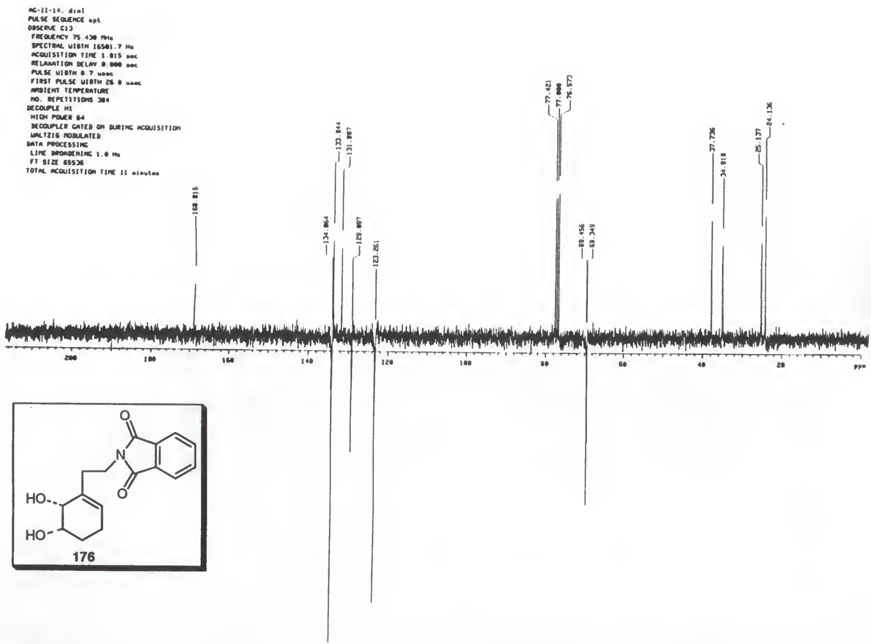
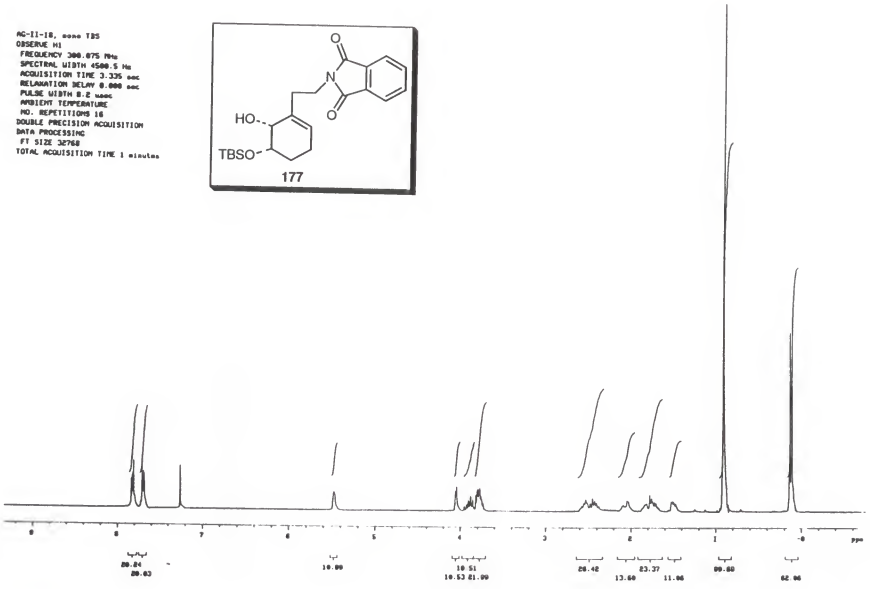
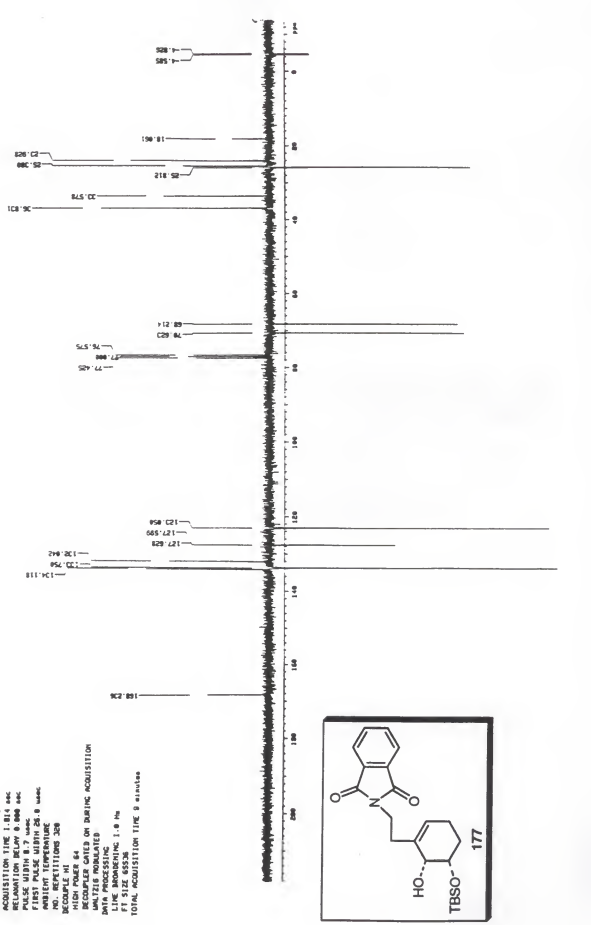
ppm
10.55
19.68
10.00
10.04
9.71
10.59
9.07
19.13
9.22
38.74
57.66


AC-1-276 phthalimide
PULSE SEQUENCE apt
OBSERVE C13
FREQUENCY 75.430 MHz
SPECTRAL WIDTH 16501.7 Hz
ACQUISITION TIME 1.815 sec
RELAXATION DELAY 0.000 sec
PULSE WIDTH 0.7 usec
FIRST PULSE WIDTH 26.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 384
DECOUPLE H1
HIGH POWER 64
DECOUPLER GATED ON DURING ACQUISITION
WALTZ16 MODULATED
DATA PROCESSING
LINE BROADENING 1.0 Hz
FT SIZE 65536
TOTAL ACQUISITION TIME 11 minutes
175
168.234
133.763
132.869
132.021
127.661
123.014
108.259
77.427
77.000
76.579
73.234
72.774
36.354
32.762
28.617
27.741
26.372
25.164
180
160
140
120
100
80
60
40
20
ppm

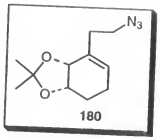

AC-II-14, diol
OBSERVE H1
FREQUENCY 299.948 MHz
SPECTRAL WIDTH 4000.0 Hz
ACQUISITION TIME 3.744 sec
RELAXATION DELAY 8.000 sec
PULSE WIDTH 7.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 16
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
FT SIZE 32768
TOTAL ACQUISITION TIME 1 minutes
HO
HO
176
9
8
7
6
5
4
3
2
1
ppm
19.68
20.12
18.06
29.77
11.83
18.05
19.99
21.81
28.84
21.43


AG-II-14. diol
PULSE SEQUENCE apt
OBSERVE C13
FREQUENCY 75.430 MHz
SPECTRAL WIDTH 16501.7 Hz
ACQUISITION TIME 1.815 sec
RELAXATION DELAY 0.000 sec
PULSE WIDTH 8.7 usec
FIRST PULSE WIDTH 26.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 384
DECOUPLE H1
HIGH POWER 64
DECOUPLER GATED ON DURING ACQUISITION
WALTZ16 MODULATED
DATA PROCESSING
LINE BROADENING 1.0 Hz
FT SIZE 65536
TOTAL ACQUISITION TIME 11 minutes
168.815
134.064
133.844
131.887
129.087
123.261
77.421
77.000
76.573
69.456
69.349
37.736
34.918
25.137
24.136
200
180
160
140
120
100
80
60
40
20
ppm
HO
HO
N
O
O
176

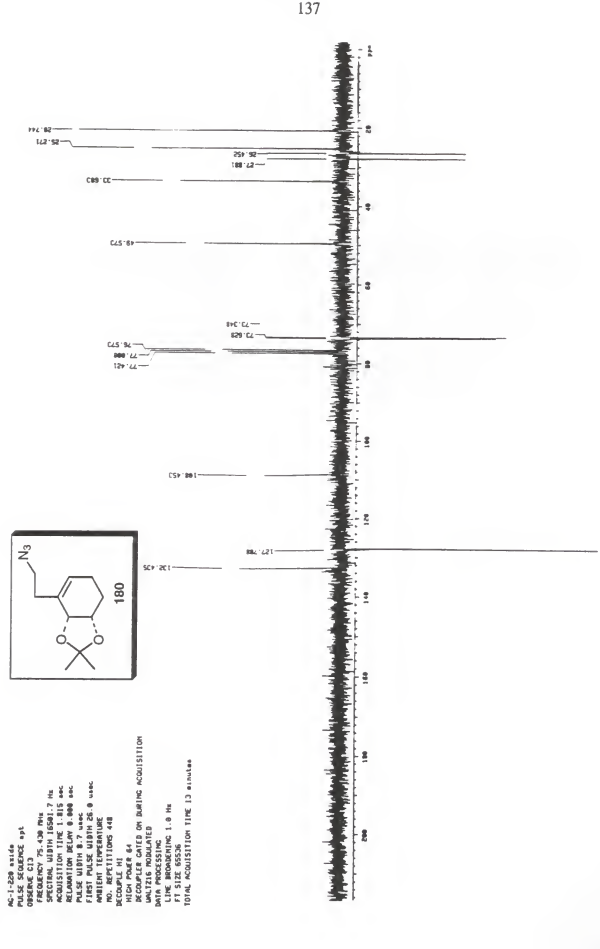

AG-II-18, acne T25
OBSERVE H1
FREQUENCY 300.075 MHz
SPECTRAL WIDTH 4500.5 Hz
ACQUISITION TIME 3.335 sec
RELAXATION DELAY 0.000 sec
PULSE WIDTH 8.2 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 16
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
FT SIZE 32768
TOTAL ACQUISITION TIME 1 minutes
HO
TBSO
177
ppm
20.04
20.03
10.00
10.51
10.53
21.99
20.42
13.60
83.37
11.06
09.80
62.96

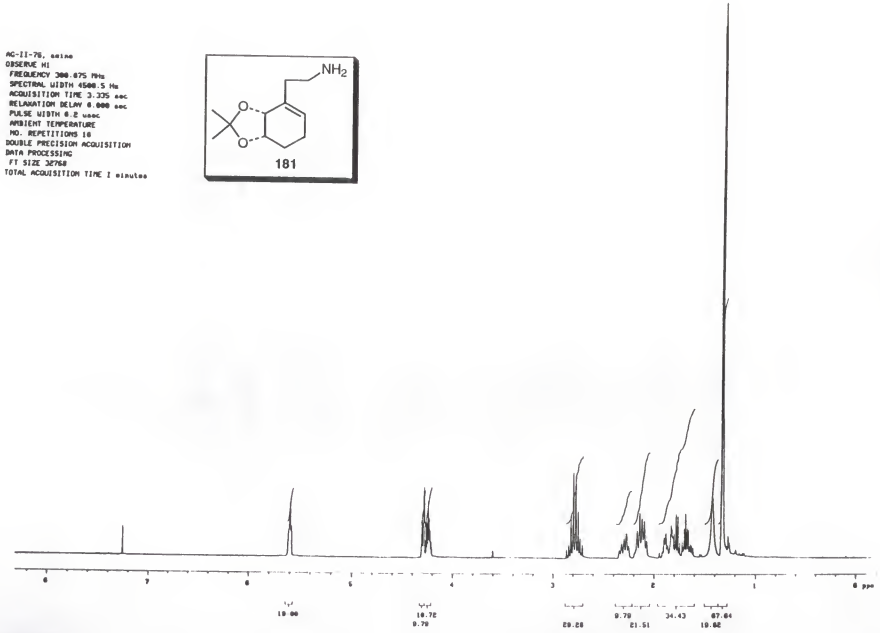

AC-II-18, mono 1H5
PULSE SEQUENCE sp1
OBSERVE C13
FREQUENCY 75.420 MHz
SPECTRAL WIDTH 17513.1 Hz
ACQUISITION TIME 1.814 sec
RECYCLE TIME 2.000 sec
PULSE WIDTH 8.7 usec
FIRST PULSE WIDTH 26.0 usec
AMBIENT TEMPERATURE
NUMBER OF SCANS 320
DECOUPLE HI
HIGH POWER 64
POWER APPLIED ON DURING ACQUISITION
WALTZ16 MODULATED
DATA PROCESSING
LINE BROADENING 1.0 Hz
FT SIZE 65536
TOTAL ACQUISITION TIME 9 minutes
HO
TBSO
177

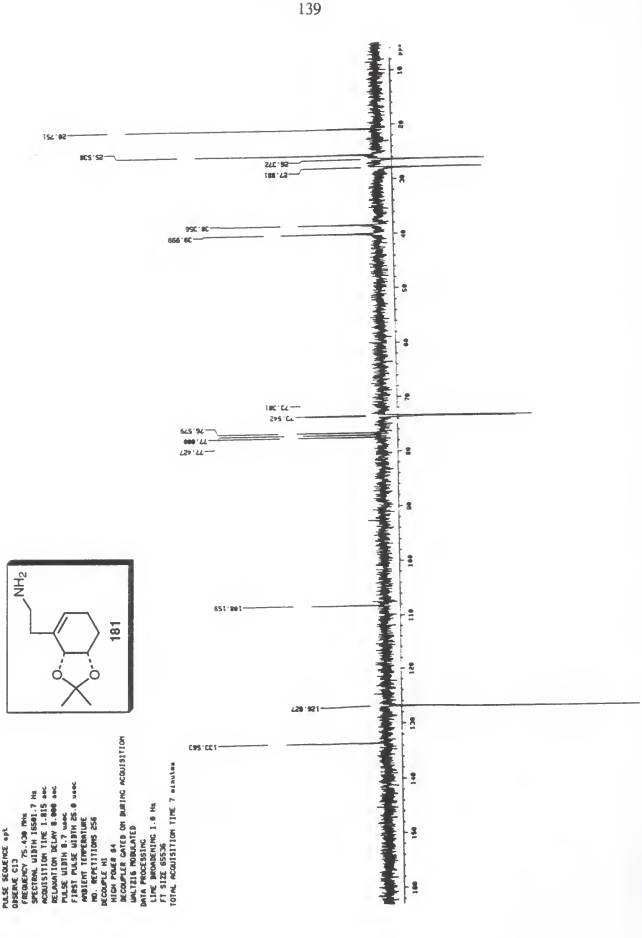
AG-I-228 azide
OBSERVE H1
FREQUENCY 299.949 MHz
SPECTRAL WIDTH 4000.0 Hz
ACQUISITION TIME 3.744 sec
RELAXATION DELAY 0.000 sec
PULSE WIDTH 7.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 16
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
FT SIZE 32768
TOTAL ACQUISITION TIME 1 minutes

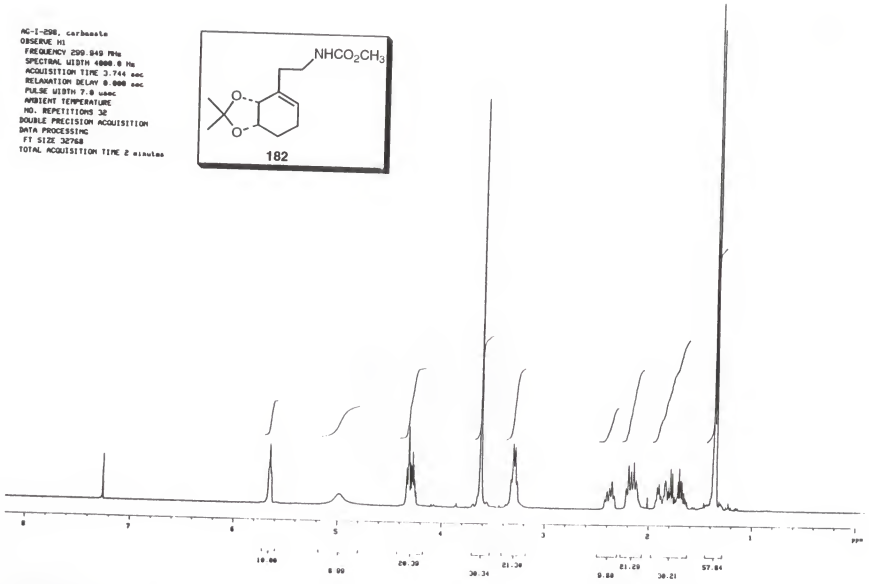


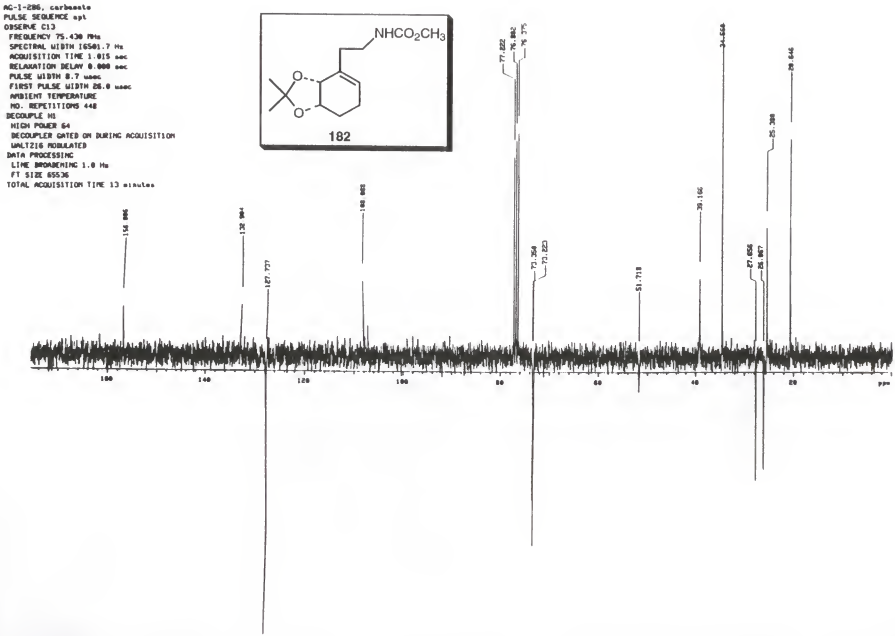
180

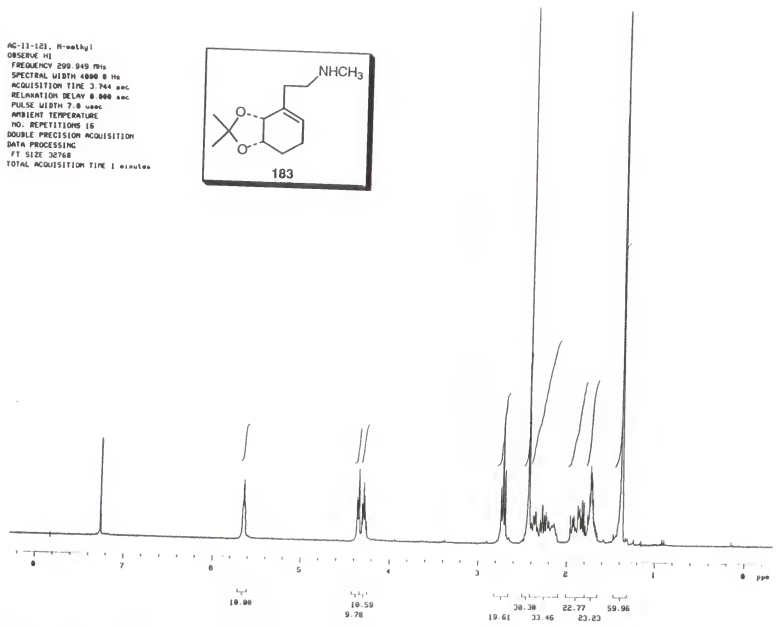

AC-1-220 acida
PULSE SEQUENCE: s2pl
OBSERVE C13
FREQUENCY 75.430 MHz
SPECTRAL WIDTH 18041.7 Hz
ACQUISITION TIME 1.818 sec
RELAXATION DELAY 0.000 sec.
PULSE WIDTH 8.7 usec
FLIP ANGLE 30 DEGREES 0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 448
DECOUPLER
HIGH POWER
DECOUPLER GATED ON DURING ACQUISITION
WALTZ16 MODULATED
DATA PROCESSING
LINE BROADENING 1.0 Hz
FT SIZE 65536
TOTAL ACQUISITION TIME 13 minutes
N3
180
28.744
32.271
33.683
69.573
73.348
73.629
76.573
77.000
77.421
168.453
127.788
132.435
ppm

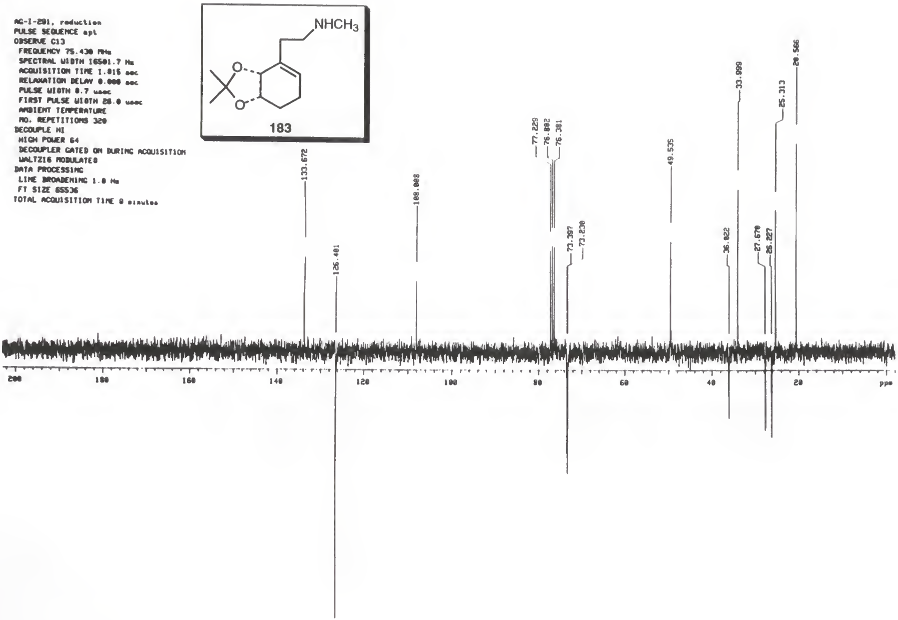

AC-II-76, amine
OBSERVE H1
FREQUENCY 300.075 MHz
SPECTRAL WIDTH 4500.5 Hz
ACQUISITION TIME 3.335 sec
RELAXATION DELAY 0.000 sec
PULSE WIDTH 8.2 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 16
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
FT SIZE 32768
TOTAL ACQUISITION TIME 1 minutes
NH2
181
10.00
10.72
9.70
29.28
9.79
21.51
34.43
67.64
19.82
ppm


AC-I-240, Anton
PULSE SEQUENCE: s2pul
OBSERVE C13
FREQUENCY 75.430 MHz
SPECTRAL WIDTH 18867.7 Hz
ACQUISITION TIME 1.815 sec.
RELAXATION DELAY 8.000 sec.
PULSE WIDTH 7
FLIP ANGLE WIDTH 25.0 usec.
AMBIENT TEMPERATURE
NO. REPETITIONS 256
DECOUPLE H1
HIGH POWER d4
DECOUPLER GATED ON DURING ACQUISITION
WAIT TIME PROGRAMMED
DATA PROCESSING
LINE BROADENING 1.0 Hz
FT SIZE 65536
TOTAL ACQUISITION TIME 7 minutes
NH2
181
133.563
128.827
108.158
77.427
77.000
76.579
73.542
73.381
39.950
38.356
28.751
25.538
25.372
23.881

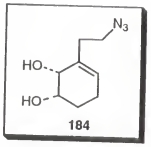

AC-I-298, carbamate
OBSERVE H1
FREQUENCY 299.949 MHz
SPECTRAL WIDTH 4000.0 Hz
ACQUISITION TIME 2.744 sec
RELAXATION DELAY 0.000 sec
PULSE WIDTH 7.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 32
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
FT SIZE 32768
TOTAL ACQUISITION TIME 2 minutes
NHCO2CH3
182
10.00
8.99
20.39
30.34
21.30
9.88
21.29
30.21
57.84
PPM


AC-I-286, carbamate
PULSE SEQUENCE apt
OBSERVE C13
FREQUENCY 75.430 MHz
SPECTRAL WIDTH 16501.7 Hz
ACQUISITION TIME 1.015 sec
RELAXATION DELAY 0.000 sec
PULSE WIDTH 8.7 usec
FIRST PULSE WIDTH 26.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 448
DECOUPLE H1
HIGH POWER 64
DECOUPLER GATED ON DURING ACQUISITION
WALTZ16 MODULATED
DATA PROCESSING
LINE BROADENING 1.0 Hz
FT SIZE 65536
TOTAL ACQUISITION TIME 13 minutes
NHCO2CH3
182
154.886
132.984
127.737
108.083
77.222
76.882
76.375
73.354
73.223
51.718
39.166
34.564
27.656
25.967
25.308
20.646
160
140
120
100
80
60
40
20
ppm

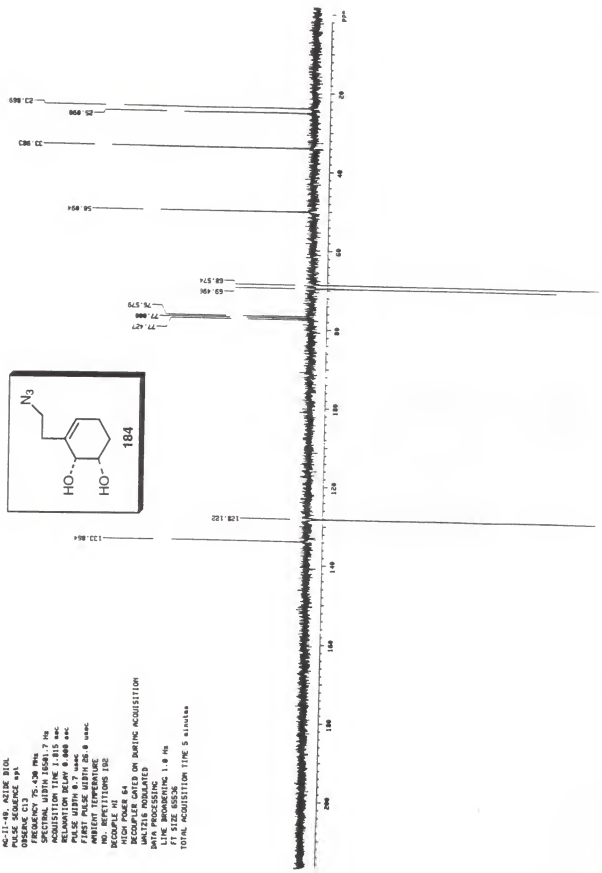

AG-II-121, N-methyl
OBSERVE H1
FREQUENCY 299.949 MHz
SPECTRAL WIDTH 4000.0 Hz
ACQUISITION TIME 3.744 sec
RELAXATION DELAY 0.000 sec
PULSE WIDTH 7.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 16
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
FT SIZE 32768
TOTAL ACQUISITION TIME 1 minutes
NHCH3
183
10.00
10.59
9.78
30.30
19.61
33.46
22.77
23.23
59.96
ppm

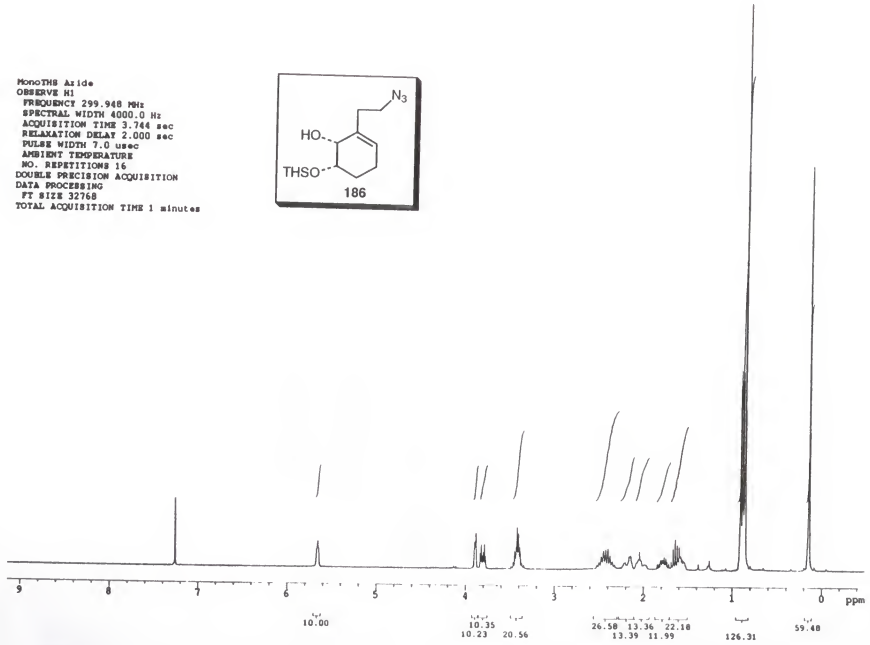

AG-I-201, reduction
PULSE SEQUENCE apt
OBSERVE C13
FREQUENCY 75.430 MHz
SPECTRAL WIDTH 16501.7 Hz
ACQUISITION TIME 1.815 sec
RELAXATION DELAY 0.000 sec
PULSE WIDTH 8.7 usec
FIRST PULSE WIDTH 26.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 320
DECOUPLE HI
HIGH POWER 64
DECOUPLER GATED ON DURING ACQUISITION
WALTZ16 MODULATED
DATA PROCESSING
LINE BROADENING 1.0 Hz
FT SIZE 65536
TOTAL ACQUISITION TIME 9 minutes
NHCH3
183
133.672
126.401
108.008
77.229
76.882
76.381
73.397
73.230
49.535
36.022
33.999
27.670
26.227
25.313
20.566
200
180
160
140
120
100
80
60
40
20
ppm

AG-II-49, azido diol
OBSERVE H1
FREQUENCY 299.949 MHz
SPECTRAL WIDTH 4000.0 Hz
ACQUISITION TIME 3.744 sec
RELAXATION DELAY 0.000 sec
PULSE WIDTH 7.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 16
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
FT SIZE 32768
TOTAL ACQUISITION TIME 1 minutes

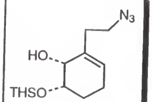


184

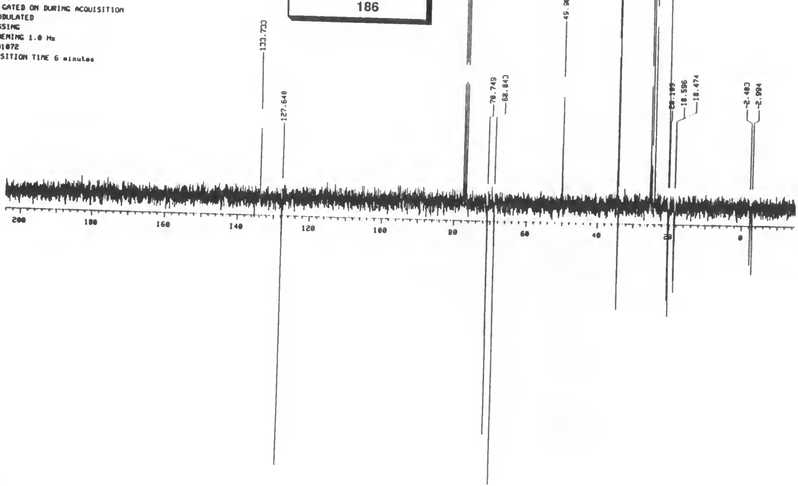

PG-II-49, AZIDE DIOL
PULSE SEQUENCE: sp1
OBSERVE C13
FREQUENCY 75.430 MHz
SPECTRAL WIDTH 18548.7 Hz
ACQUISITION TIME 2.161 sec
RELAXATION DELAY 0.000 sec
PULSE WIDTH 8.7 usec
FLIP ANGLE 30 DEGREE
AMBIENT TEMPERATURE
NO. REPETITIONS 192
DATA POINTS 64
DECOUPLER GATED ON DURING ACQUISITION
ANALYZE MODULATED
WEIGHTING FUNCTION
LINE BROADENING 1.0 Hz
FT SIZE 65536
TOTAL ACQUISITION TIME 5 minutes
184
N3
HO
HO
133.864
121.821
77.427
77.000
76.579
69.574
63.496
56.854
33.983
23.869

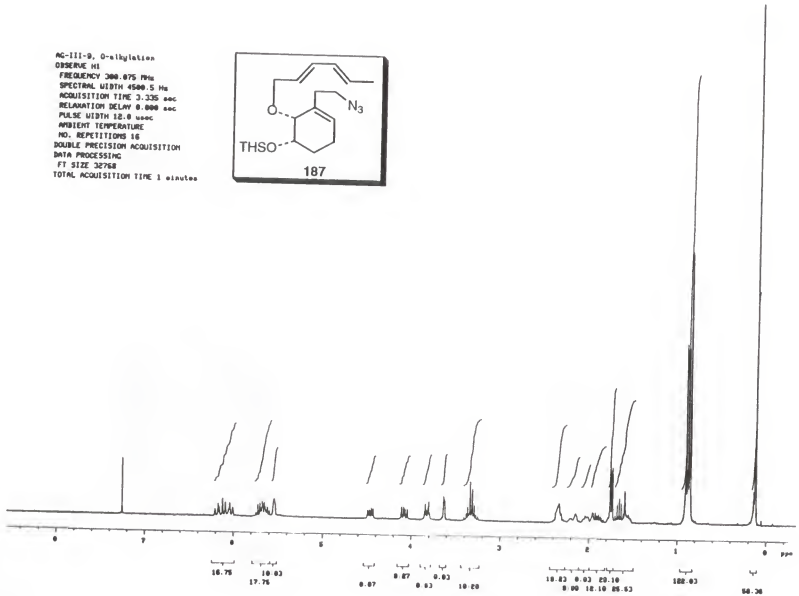

MonoTHS Azide
OBSERVE H1
FREQUENCY 299.948 MHz
SPECTRAL WIDTH 4000.0 Hz
ACQUISITION TIME 3.744 sec
RELAXATION DELAY 2.000 sec
PULSE WIDTH 7.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 16
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
FT SIZE 32768
TOTAL ACQUISITION TIME 1 minutes
N3
HO
THSO
186
9
8
7
6
5
4
3
2
1
0
ppm
10.00
10.35
10.23
20.56
26.58
13.39
13.36
11.99
22.18
126.31
59.48

AG-II-115, THSprotected
PULSE SEQUENCE apt
OBSERVE C13
FREQUENCY 75.427 MHz
SPECTRAL WIDTH 20000.0 Hz
ACQUISITION TIME 1.920 sec
RELAXATION DELAY 0.000 sec
PULSE WIDTH 0.7 usec
FIRST PULSE WIDTH 26.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 192
DECOUPLE H1
HIGH POWER 64
DECOUPLER GATED ON DURING ACQUISITION
WALTZ16 MODULATED
DATA PROCESSING
LINE BROADENING 1.0 Hz
FT SIZE 131072
TOTAL ACQUISITION TIME 6 minutes

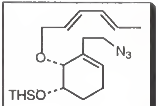


186

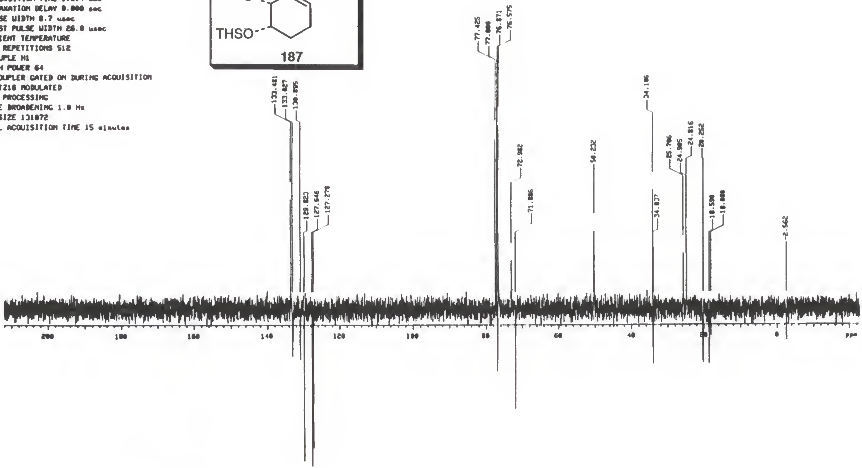



AG-III-9, O-alkylation
OBSERVE H1
FREQUENCY 300.075 MHz
SPECTRAL WIDTH 4500.5 Hz
ACQUISITION TIME 3.335 sec
RELAXATION DELAY 0.000 sec
PULSE WIDTH 12.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 16
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
FT SIZE 32768
TOTAL ACQUISITION TIME 1 minutes
N3
THSO
187
ppm

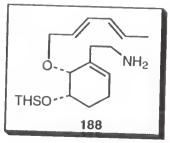
AG-II-129
PULSE SEQUENCE apt
OBSERVE C13
FREQUENCY 75.430 MHz
SPECTRAL WIDTH 20000.0 Hz
ACQUISITION TIME 1.814 sec
RELAXATION DELAY 0.000 sec
PULSE WIDTH 8.7 usec
FIRST PULSE WIDTH 26.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 512
DECOUPLE H1
HIGH POWER 64
DECOUPLER GATED ON DURING ACQUISITION
WALTZ16 MODULATED
DATA PROCESSING
LINE BROADENING 1.0 Hz
FT SIZE 131072
TOTAL ACQUISITION TIME 15 minutes



187

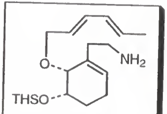


AG-III-10, amine
OBSERVE H1
FREQUENCY 250.848 MHz
SPECTRAL WIDTH 4000.0 Hz
ACQUISITION TIME 3.744 sec
RELAXATION DELAY 0.000 sec
PULSE WIDTH 7.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 16
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
FT SIZE 32768
TOTAL ACQUISITION TIME 1 minutes

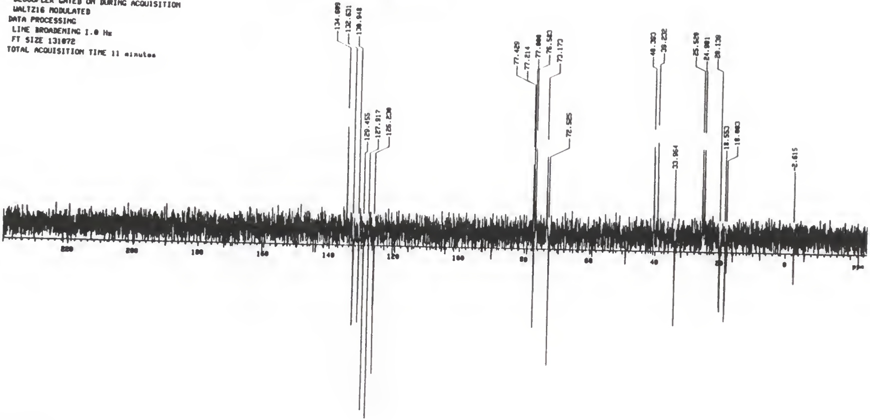


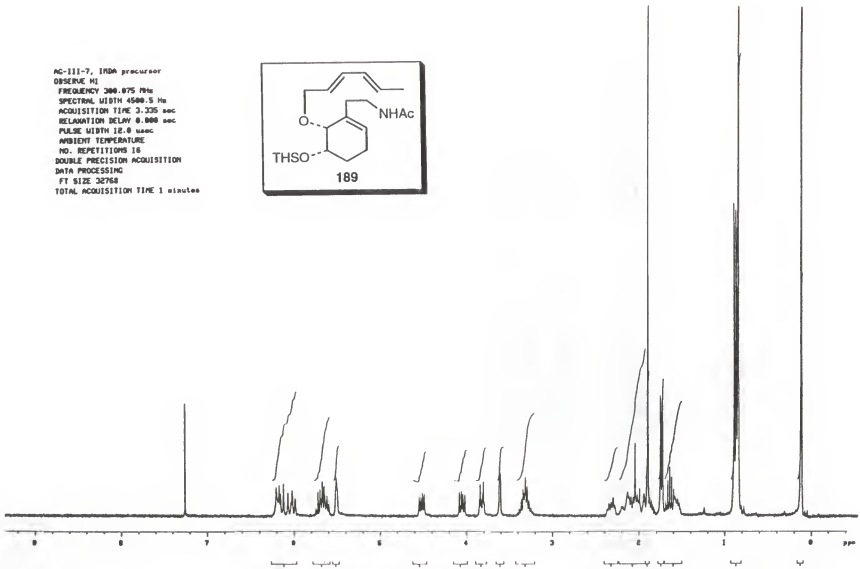
188

AG-III-10, amine
PULSE SEQUENCE apt
OBSERVE C13
FREQUENCY 75.430 MHz
SPECTRAL WIDTH 20000.0 Hz
ACQUISITION TIME 1.814 sec
RELAXATION DELAY 0.000 sec
PULSE WIDTH 8.7 usec
FIRST PULSE WIDTH 26.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 384
DECOUPLE H1
HIGH POWER 64
DECOUPLER GATED ON DURING ACQUISITION
WALTZ16 MODULATED
DATA PROCESSING
LINE BROADENING 1.0 Hz
FT SIZE 131072
TOTAL ACQUISITION TIME 11 minutes

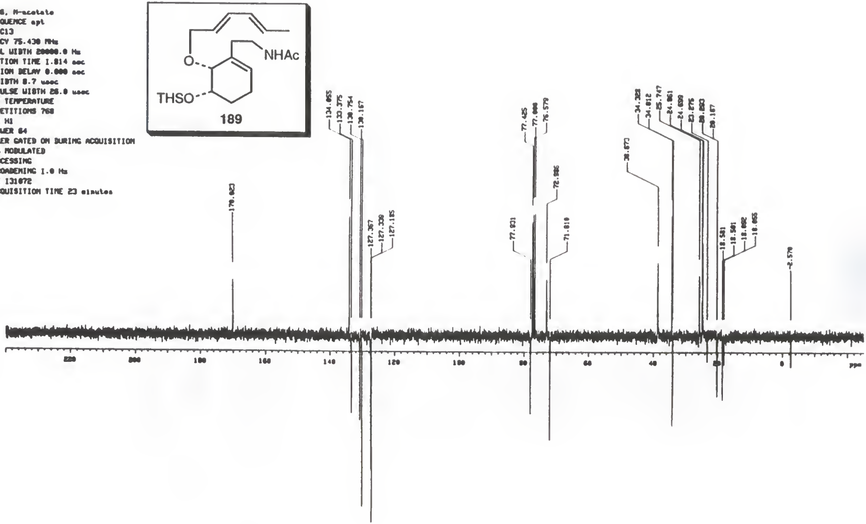


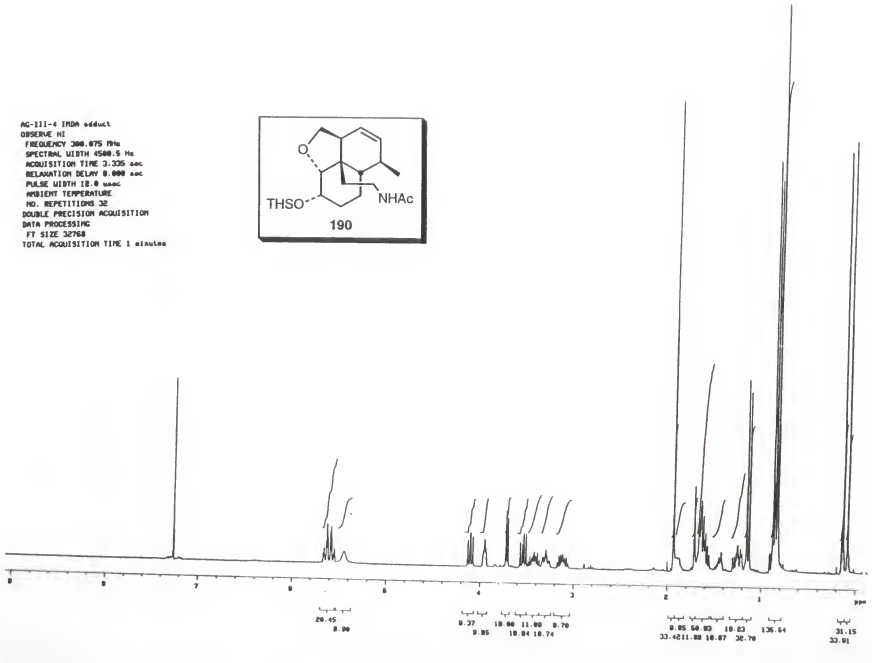
188



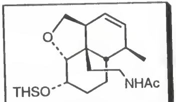

AG-III-7, INDA precursor
OBSERVE H1
FREQUENCY 300.075 MHz
SPECTRAL WIDTH 4500.5 Hz
ACQUISITION TIME 3.335 sec
RELAXATION DELAY 0.000 sec
PULSE WIDTH 12.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 16
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
FT SIZE 32768
TOTAL ACQUISITION TIME 1 minutes
NHAc
O
THSO
189
ppm
25.78
10.00
10.41
0.17
0.63
0.30
0.58
10.51
0.40
32.14
23.03
30.90
29.97
186.21
91.81

AG-II-138, N-acetate
PULSE SEQUENCE apt
OBSERVE C13
FREQUENCY 75.430 MHz
SPECTRAL WIDTH 20000.0 Hz
ACQUISITION TIME 1.814 sec
RELAXATION DELAY 0.000 sec
PULSE WIDTH 8.7 usec
FIRST PULSE WIDTH 26.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 768
DECOUPLE H1
HIGH POWER 64
DECOUPLER GATED ON DURING ACQUISITION
WALTZ16 MODULATED
DATA PROCESSING
LINE BROADENING 1.0 Hz
FT SIZE 131072
TOTAL ACQUISITION TIME 23 minutes

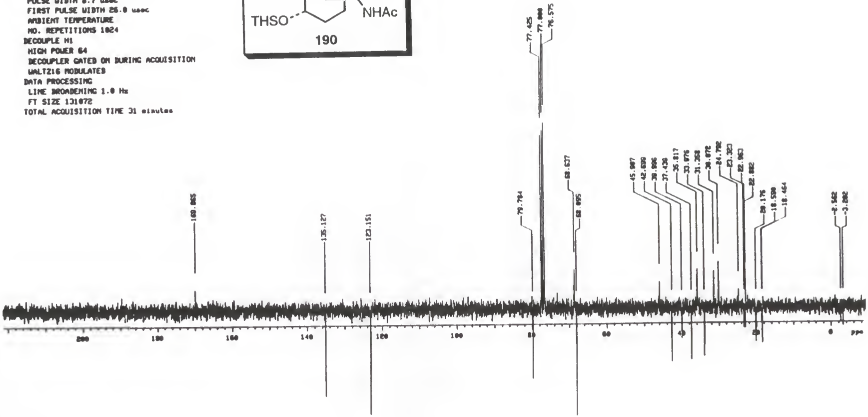


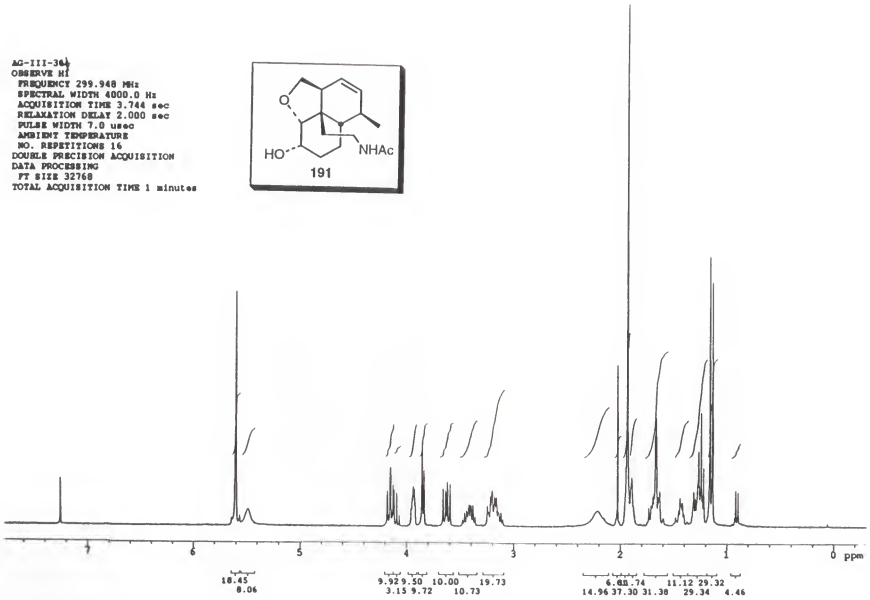

AG-III-4 IMDA adduct
OBSERVE H1
FREQUENCY 300.075 MHz
SPECTRAL WIDTH 4500.5 Hz
ACQUISITION TIME 3.335 sec
RELAXATION DELAY 0.000 sec
PULSE WIDTH 12.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 32
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
FT SIZE 32768
TOTAL ACQUISITION TIME 1 minutes
O
THSO
NHAc
190
ppm

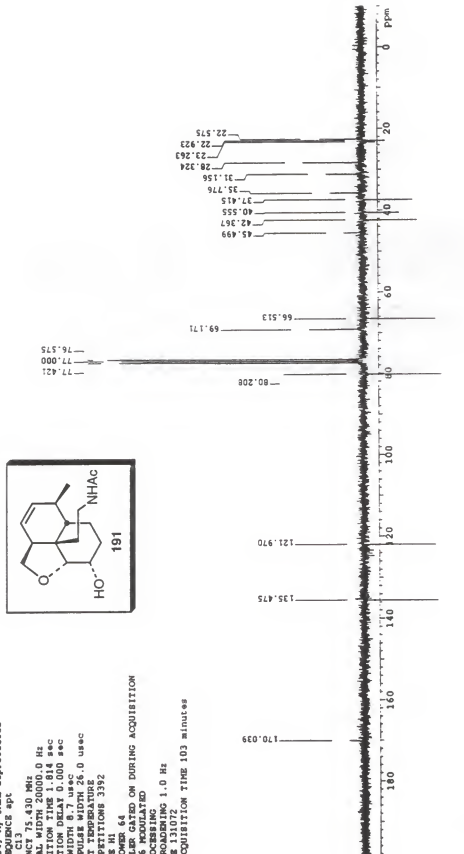
AG-III-4, IMDA Adduct, APT
PULSE SEQUENCE apt
OBSERVE C13
FREQUENCY 75.430 MHz
SPECTRAL WIDTH 20000.0 Hz
ACQUISITION TIME 1.014 sec
RELAXATION DELAY 0.000 sec
PULSE WIDTH 8.7 usec
FIRST PULSE WIDTH 25.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 1024
DECOUPLE H1
HIGH POWER 64
DECOUPLER GATED ON DURING ACQUISITION
WALTZ16 MODULATED
DATA PROCESSING
LINE BROADENING 1.0 Hz
FT SIZE 131072
TOTAL ACQUISITION TIME 31 minutes



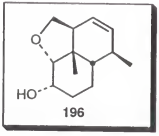
190



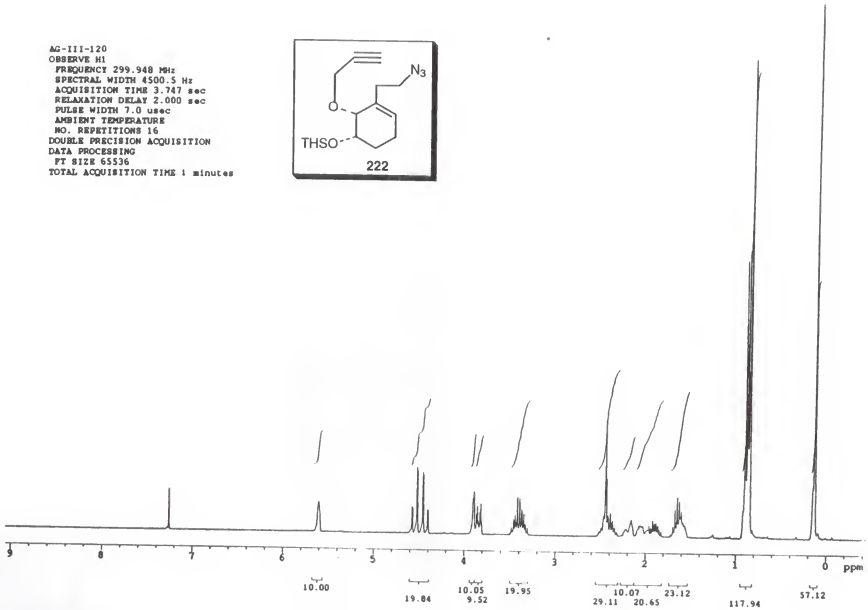

AG-III-36
OBSERVE H1
FREQUENCY 299.948 MHz
SPECTRAL WIDTH 4000.0 Hz
ACQUISITION TIME 3.744 sec
RELAXATION DELAY 2.000 sec
PULSE WIDTH 7.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 16
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
FT SIZE 32768
TOTAL ACQUISITION TIME 1 minutes
O
HO
NHAc
191
7
6
5
4
3
2
1
0 ppm
18.45
8.06
9.92 9.50 10.00 19.73
3.15 9.72 10.73
6.88 6.74 11.12 29.32
14.96 37.30 31.38 29.34 4.46


AC-III-34, My IMDA deprotected
PULSE SEQUENCE apt
OBSERVE C13
FREQUENCY 75.430 MHz
SPECTRAL WIDTH 20000.0 Hz
ACQUISITION TIME 1.814 sec
RELAXATION DELAY 0.000 sec
PULSE WIDTH 8.7 usec
FIRST PULSE WIDTH 8.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 3392
DECOUPLE H1
POWER 64
DECOUPLER GATED ON DURING ACQUISITION
WALTZ16 MODULATED
DATA PROCESSING
LINE BROADENING 1.0 Hz
FT SIZE 131072
TOTAL ACQUISITION TIME 103 minutes
NHAc
HO
191
170.039
135.475
121.970
80.208
77.421
77.000
76.575
69.171
66.513
45.499
42.367
40.555
37.415
35.776
31.156
28.324
23.263
22.923
22.575
ppm

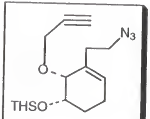
AG-III-28, Boroo IMDA adduct deprotected
OBSERVE H1
FREQUENCY 298.948 MHz
SPECTRAL WIDTH 4000.0 Hz
ACQUISITION TIME 3.744 sec
RELAXATION DELAY 9.000 sec
PULSE WIDTH 7.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 16
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
FT SIZE 32768
TOTAL ACQUISITION TIME 1 minutes



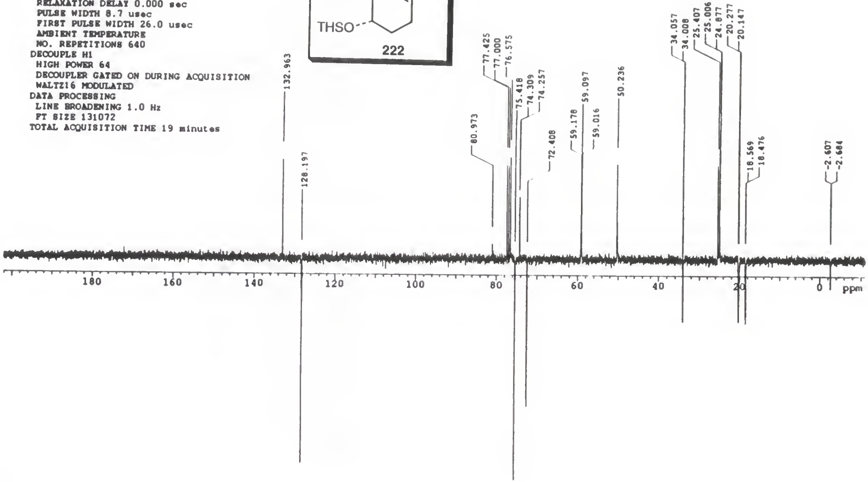
AC-III-28, Boron ION Adduct Deprotected
PULSE SEQUENCE: s2pul
OBSERVE C13
FREQUENCY 75.430 MHz
SPECTRAL WIDTH 18940.7 Hz
ACQUISITION TIME 1.615 sec
RELAXATION DELAY 0.000 sec
PULSE WIDTH 9.7 usec
PULSE WIDTH 90 DEGREES 19.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 320
RECEIVER GAIN
HIGH POWER 64
DECOUPLER GATED ON DURING ACQUISITION
SAMPLE REMOVED
DATA PROCESSING
LINE BROADENING 1.0 Hz
FT SIZE 65536
TOTAL ACQUISITION TIME 9 minutes
HO
196
135.812
122.280
84.257
77.421
76.573
69.589
66.431
47.744
42.883
38.692
37.258
28.468
23.174
22.760
ppm

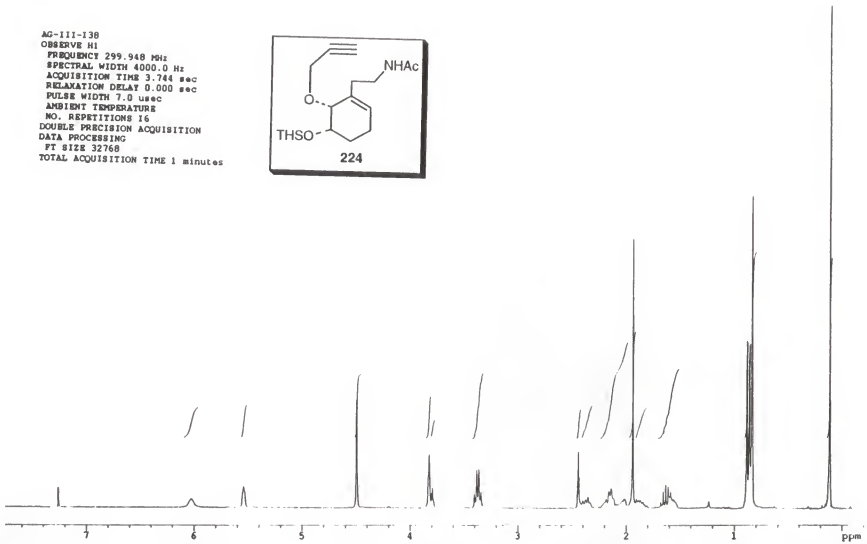

AG-III-120
OBSERVE H1
FREQUENCY 299.948 MHz
SPECTRAL WIDTH 4500.5 Hz
ACQUISITION TIME 3.747 sec
RELAXATION DELAY 2.000 sec
PULSE WIDTH 7.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 16
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
FT SIZE 65536
TOTAL ACQUISITION TIME 1 minutes
N3
THSO
222
9
8
7
6
5
4
3
2
1
0
ppm
10.00
19.84
10.05
9.52
19.95
10.07
29.11
20.65
23.12
117.94
57.12

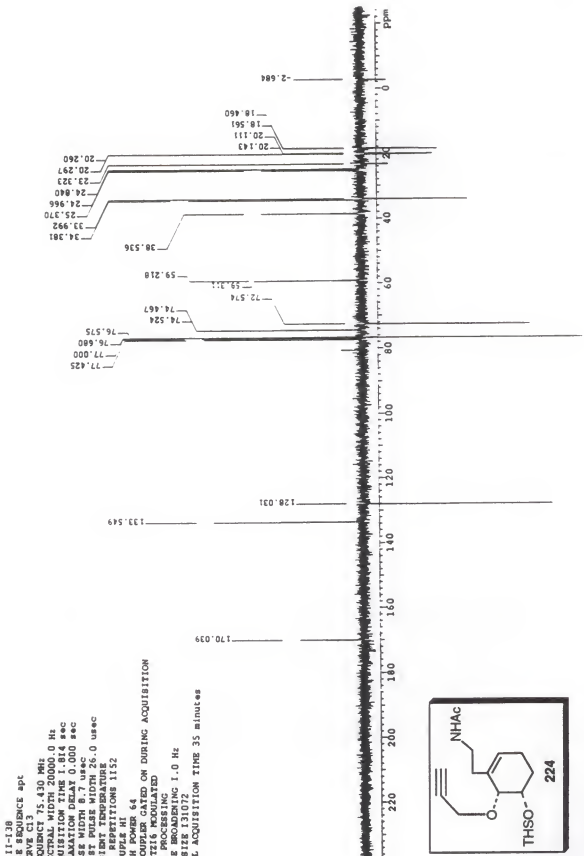
AG-III-120, alkyne
PULSE SEQUENCE apt
OBSERVE C13
FREQUENCY 75.430 MHz
SPECTRAL WIDTH 20000.0 Hz
ACQUISITION TIME 1.814 sec
RELAXATION DELAY 0.000 sec
PULSE WIDTH 8.7 usec
FIRST PULSE WIDTH 26.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 640
DECOUPLE H1
HIGH POWER 64
DECOUPLER GATED ON DURING ACQUISITION
WALTZ16 MODULATED
DATA PROCESSING
LINE BROADENING 1.0 Hz
FT SIZE 131072
TOTAL ACQUISITION TIME 19 minutes

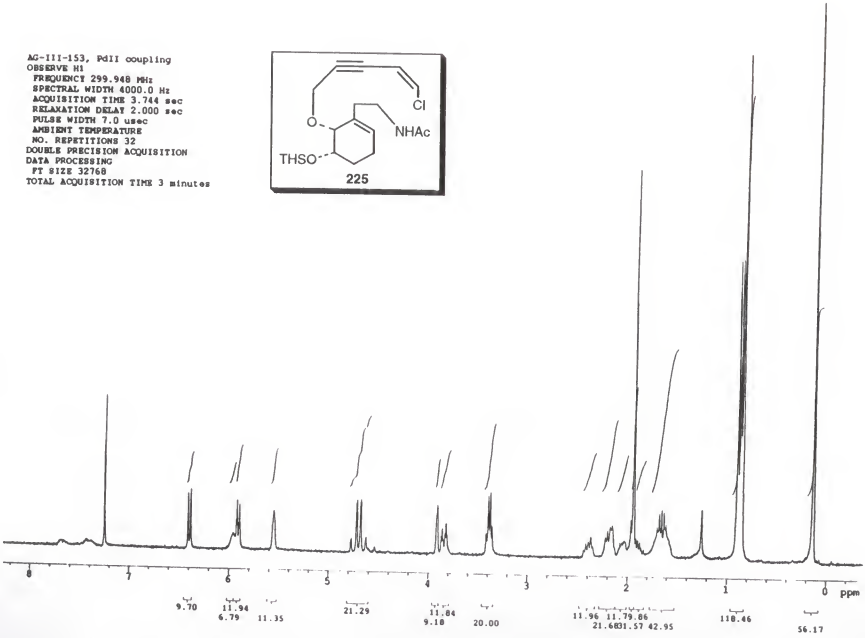


222



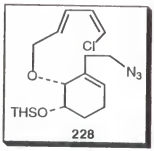

AG-III-138
OBSERVE H1
FREQUENCY 299.948 MHz
SPECTRAL WIDTH 4000.0 Hz
ACQUISITION TIME 3.744 sec
RELAXATION DELAY 0.000 sec
PULSE WIDTH 7.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 16
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
FT SIZE 32768
TOTAL ACQUISITION TIME 1 minutes
NHAc
O
THSO
224
7
6
5
4
3
2
1
Ppm
9.29
10.00
10.84
5.68
13.42
19.34
9.16
20.80
10.01
10.00
31.99
20.46
25.56
29.67
54.01


AG-III-138
PULSE SEQUENCE apt
OBSERVE C13
FREQUENCY 75.430 MHz
SPECTRAL WIDTH 20000.0 Hz
ACQUISITION TIME 1.814 sec
RELAXATION DELAY 0.000 sec
PULSE REPETITION 2.000 sec
FIRST PULSE WIDTH 26.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 1152
DECOUPLER FREQUENCY
HIGH POWER 64
DECOUPLER GATED ON DURING ACQUISITION
WALTZ16 MODULATED
DATA PROCESSING
LINE BROADENING 1.0 Hz
FT SIZE 131072
TOTAL ACQUISITION TIME 35 minutes
-2.684
18.460
18.561
20.111
20.143
20.260
20.297
23.323
24.040
24.966
25.370
33.992
34.381
38.536
59.218
59.311
72.574
74.467
74.524
76.575
76.680
77.000
77.425
128.031
133.549
170.039
ppm
NHAc
O
THSO
224


AG-III-153, PdII coupling
OBSERVE H1
FREQUENCY 299.948 MHz
SPECTRAL WIDTH 4000.0 Hz
ACQUISITION TIME 3.744 sec
RELAXATION DELAY 2.000 sec
PULSE WIDTH 7.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 32
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
FT SIZE 32768
TOTAL ACQUISITION TIME 3 minutes
Cl
NHAc
O
THSO
225
9.70
11.94
6.79
11.35
21.29
11.84
9.18
20.00
11.96
11.79
21.68
31.57
42.95
110.46
56.17
ppm

AC-III-153, Pd11 Coupled product
OBSERVE C13
FREQUENCY 75.462 MHz
SPECTRAL WIDTH 20000.0 Hz
ACQUISITION TIME 1.7039 sec
RELAXATION DELAY 0.000 sec
PULSE WIDTH 5.0 usec
AMBIENT TEMPERATURE
NUMBER OF TRANSIENTS 7680
DECOUPLE HI
LOW POWER 1023
DECOUPLER COMPLEXMODULT ON
WALTZ MODULATED
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
LINE BROADENING 3.5 Hz
FT SIZE 32768
TOTAL ACQUISITION TIME 102 minutes
Cl
NHAc
THSO
O
225
170.182
133.621
128.784
128.153
111.603
94.472
82.333
72.648
59.836
38.708
34.637
34.033
25.443
25.006
23.243
20.314
20.201
18.600
18.503
-2.577
ppm

AG-III-202, terminal Cl triene
OBSERVE H1
FREQUENCY 300.075 MHz
SPECTRAL WIDTH 4500.5 Hz
ACQUISITION TIME 1.998 sec
RELAXATION DELAY 2.000 sec
PULSE WIDTH 5.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 16
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
LINE BROADENING 1.0 Hz
FT SIZE 32768
TOTAL ACQUISITION TIME 1 minutes



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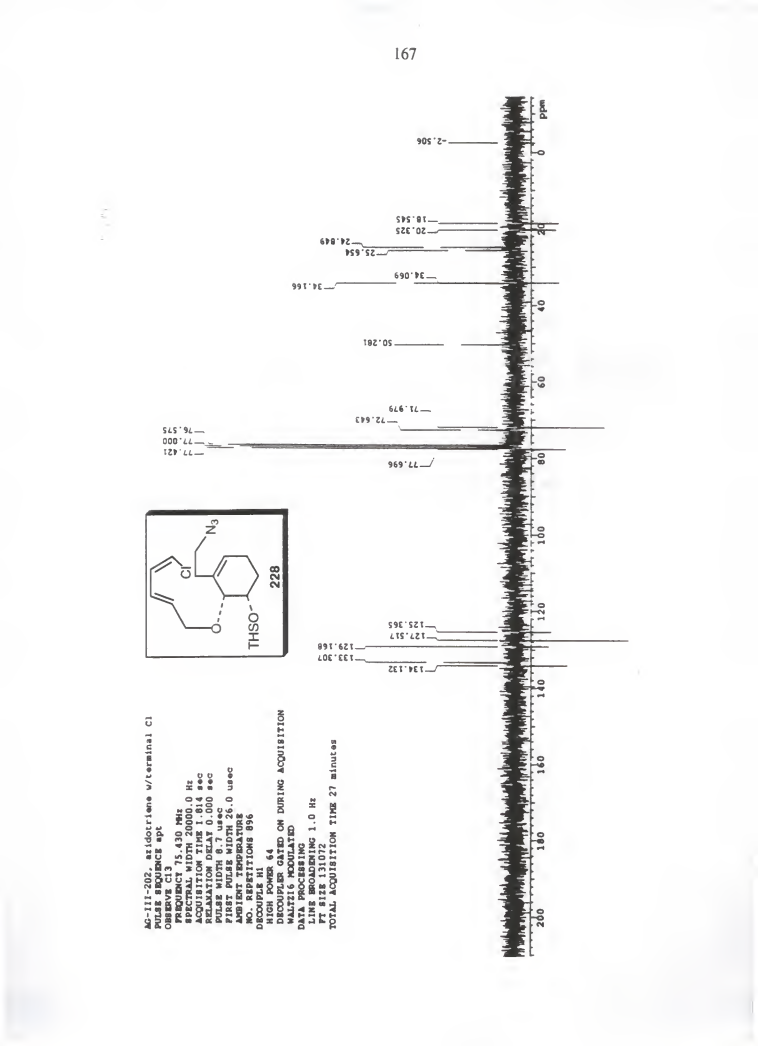
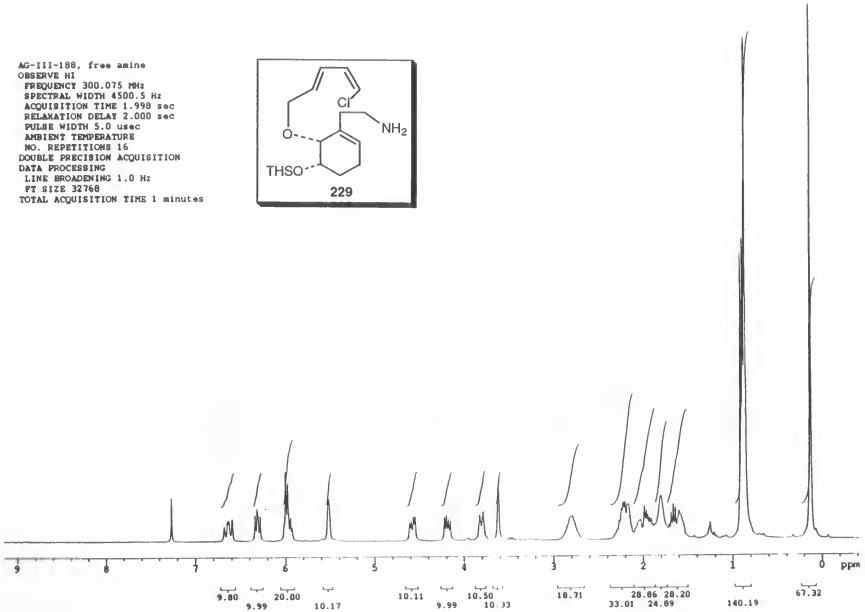
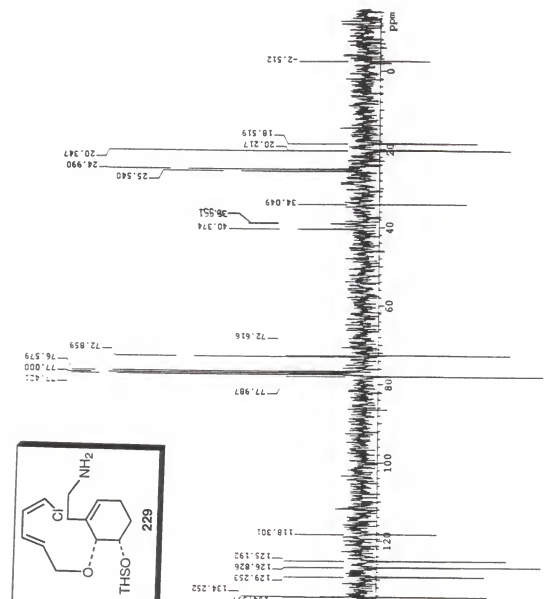
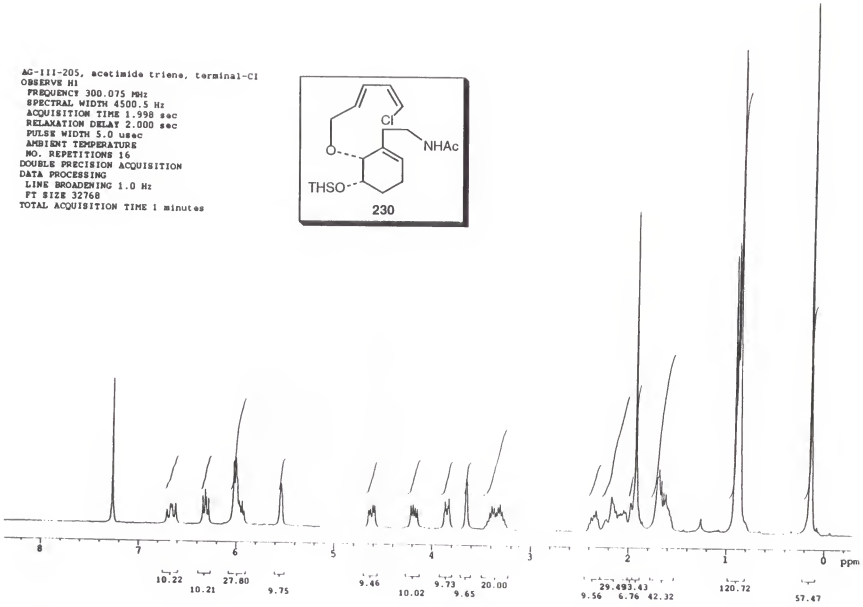
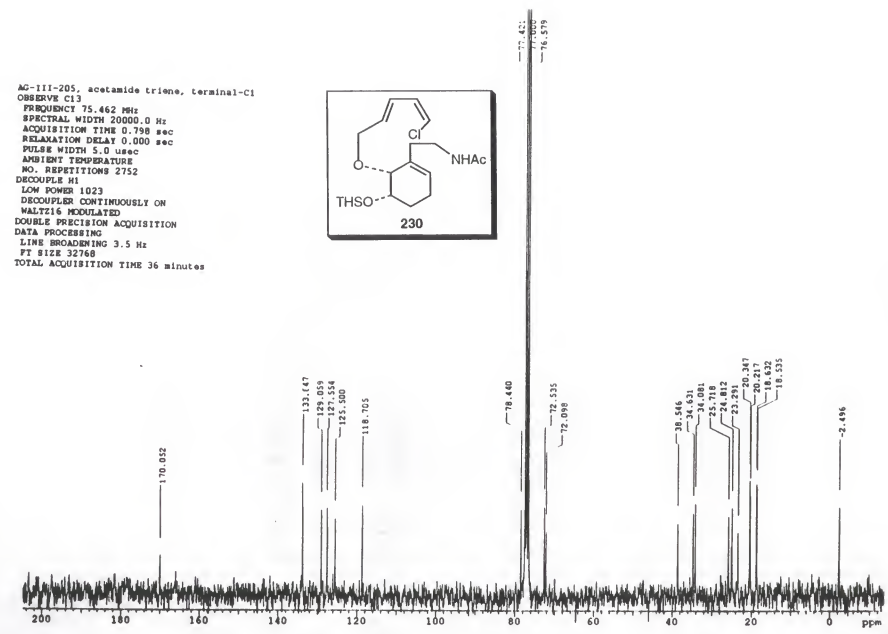

AG-III-202, azidotriene w/terminal Cl
PULSE SEQUENCE apt
CARBON-13
FREQUENCY 75.430 MHz
SPECTRAL WIDTH 20000.0 Hz
ACQUISITION TIME 1.814 sec
RELAXATION DELAY 0.000 sec
PULSE WIDTH 8.7 usec
FIRST PULSE WIDTH 26.0 usec
NO. REPETITIONS 896
DECOUPLE HI
HIGH POWER 64
DECOUPLER TURNED ON DURING ACQUISITION
WALTZ16 MODULATED
DATA PROCESSING
LINE BROADENING 1.0 Hz
FT SIZE 131072
TOTAL ACQUISITION TIME 27 minutes
Cl
N3
O
THSO
228
77.421
77.000
76.575
77.696
72.463
71.979
50.281
34.166
34.069
25.654
24.849
20.325
18.545
-2.506
134.132
133.307
129.168
127.517
125.365
ppm

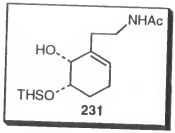

AG-III-188, free amine
OBSERVE H1
FREQUENCY 300.075 MHz
SPECTRAL WIDTH 4500.5 Hz
ACQUISITION TIME 1.998 sec
RELAXATION DELAY 2.000 sec
PULSE WIDTH 5.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 16
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
LINE BROADENING 1.0 Hz
FT SIZE 32768
TOTAL ACQUISITION TIME 1 minutes
Cl
NH2
O
THSO
229
9
8
7
6
5
4
3
2
1
0
ppm
9.80
9.99
20.00
10.17
10.11
9.99
10.50
10.33
18.71
33.01
28.86
24.89
28.20
140.19
67.32


AC-III-189, free amine
PULSE SEQUENCE zgpg
OBSERVE C13
FREQUENCY 75.462 MHz
SPECTRAL WIDTH 20000.0 Hz
ACQUISITION TIME 0.798 sec
RELAXATION DELAY 2.000 sec
PULSE WIDTH 5.0 usec
FIRST PULSE WIDTH 31.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 1792
DECOUPLE H1
H1 FREQUENCY 300.13
DECOUPLER GATED ON DURING ACQUISITION
WALTZ16 MODULATED
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
LINE BROADENING 3.5 Hz
FT SIZE 32768
TOTAL ACQUISITION TIME 24 minutes
NH2
Cl
O
THSO
229
77.422
77.000
76.579
72.859
72.616
77.987
40.374
38.551
34.049
25.560
24.990
20.347
20.217
18.519
-2.512
134.397
134.252
129.253
126.826
125.192
118.301
ppm


AG-III-205, acetimide triene, terminal-Cl
OBSERVE H1
FREQUENCY 300.075 MHz
SPECTRAL WIDTH 4500.5 Hz
ACQUISITION TIME 1.998 sec
RELAXATION DELAY 2.000 sec
PULSE WIDTH 5.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 16
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
LINE BROADENING 1.0 Hz
FT SIZE 32768
TOTAL ACQUISITION TIME 1 minutes
Cl
NHAc
O
THSO
230
8
7
6
5
4
3
2
1
0
ppm
10.22
10.21
27.80
9.75
9.46
10.02
9.73
9.65
20.00
9.56
6.76
29.49
3.43
42.32
120.72
57.47


AG-III-205, acetamide triene, terminal-Cl
OBSERVE C13
FREQUENCY 75.462 MHz
SPECTRAL WIDTH 20000.0 Hz
ACQUISITION TIME 0.798 sec
RELAXATION DELAY 0.000 sec
PULSE WIDTH 5.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 2752
DECOUPLE H1
LOW POWER 1023
DECOUPLER CONTINUOUSLY ON
WALTZ16 MODULATED
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
LINE BROADENING 3.5 Hz
FT SIZE 32768
TOTAL ACQUISITION TIME 36 minutes
Cl
NHAc
O
THSO
230
77.421
77.000
76.579
170.052
133.647
129.059
127.554
125.500
118.705
78.460
72.535
72.090
38.546
36.631
34.081
25.718
24.812
23.252
20.347
20.217
18.632
18.535
-2.496
200
180
160
140
120
100
80
60
40
20
0
ppm

AG-III-80, THS protected acetamide
OBSERVE H1
FREQUENCY 299.948 MHz
SPECTRAL WIDTH 4000.0 Hz
ACQUISITION TIME 3.744 sec
RELAXATION DELAY 2.000 sec
PULSE WIDTH 7.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 16
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
FT SIZE 32768
TOTAL ACQUISITION TIME 1 minutes



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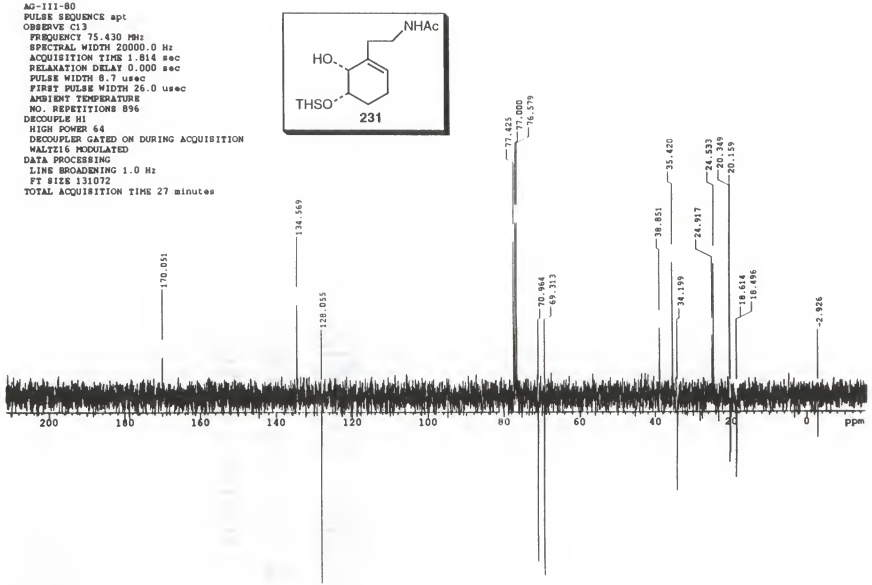
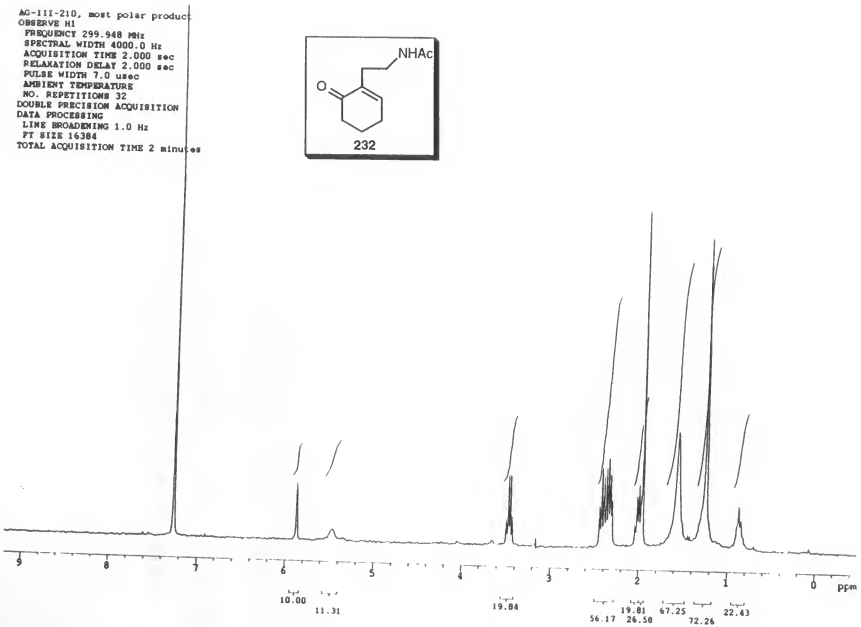
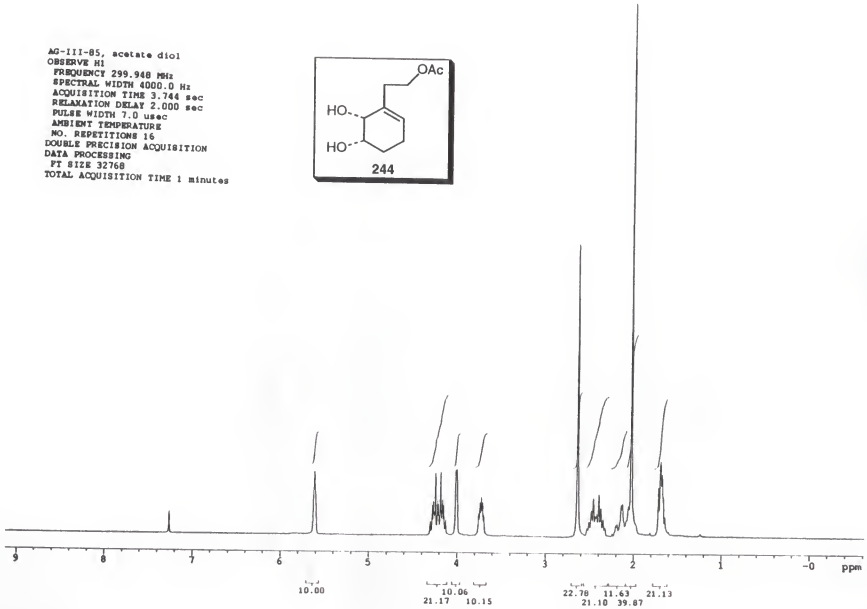
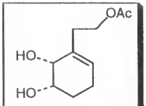

AG-III-80
PULSE SEQUENCE apt
OBSERVE C13
FREQUENCY 75.430 MHz
SPECTRAL WIDTH 20000.0 Hz
ACQUISITION TIME 1.814 sec
RELAXATION DELAY 0.000 sec
PULSE WIDTH 8.7 usec
FIRST PULSE WIDTH 26.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 896
DECOUPLE H1
HIGH POWER 64
DECOUPLER GATED ON DURING ACQUISITION
WALTZ16 MODULATED
DATA PROCESSING
LINE BROADENING 1.0 Hz
FT SIZE 131072
TOTAL ACQUISITION TIME 27 minutes
NHAc
HO
THSO
231
77.425
77.000
76.579
70.864
69.313
35.420
30.851
24.917
24.593
24.349
20.159
18.614
18.496
34.199
170.051
134.569
120.055
-2.926
200
180
160
140
120
100
80
60
40
20
0
ppm


AG-III-210, most polar product
OBSERVE H1
FREQUENCY 299.948 MHz
SPECTRAL WIDTH 4000.0 Hz
ACQUISITION TIME 2.000 sec
RELAXATION DELAY 2.000 sec
PULSE WIDTH 7.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 32
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
LINE BROADENING 1.0 Hz
FT SIZE 16384
TOTAL ACQUISITION TIME 2 minutes
NHAc
O
232
9
8
7
6
5
4
3
2
1
0
ppm
10.00
11.31
19.84
56.17
19.81
26.50
67.25
72.26
22.43

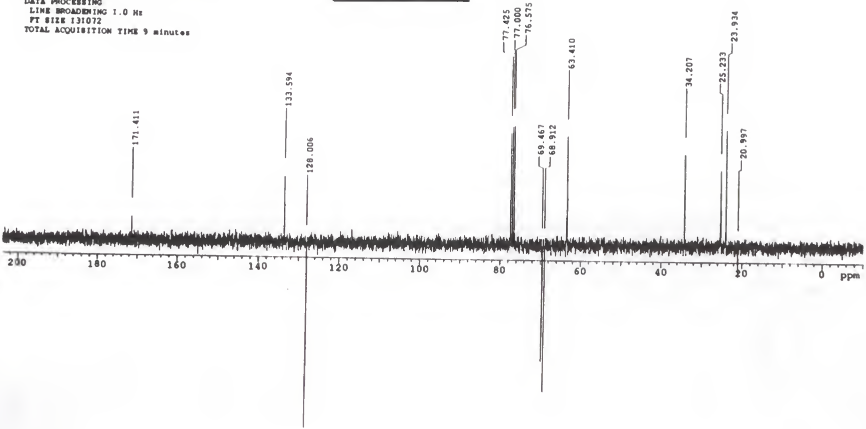
Ag-III-210 most polar product
OBSERVE C13
FREQUENCY 75.430 MHz
SPECTRAL WIDTH 4401.7 Hz
ACQUISITION TIME 1.815 sec
RELAXATION DELAY 0.000 sec
PULSE WIDTH 8.7 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 16448
DECOUPLE H1
HIGH POWER
DECOUPLER CONTINUOUSLY ON
WALTZ16 MODULATED
DATA PROCESSING
FT SIZE 65536
TOTAL ACQUISITION TIME 8.3 hours
NHAc
232
126.967
77.423
77.000
76.573
37.983
37.242
36.754
29.697
29.390
22.607
ppm

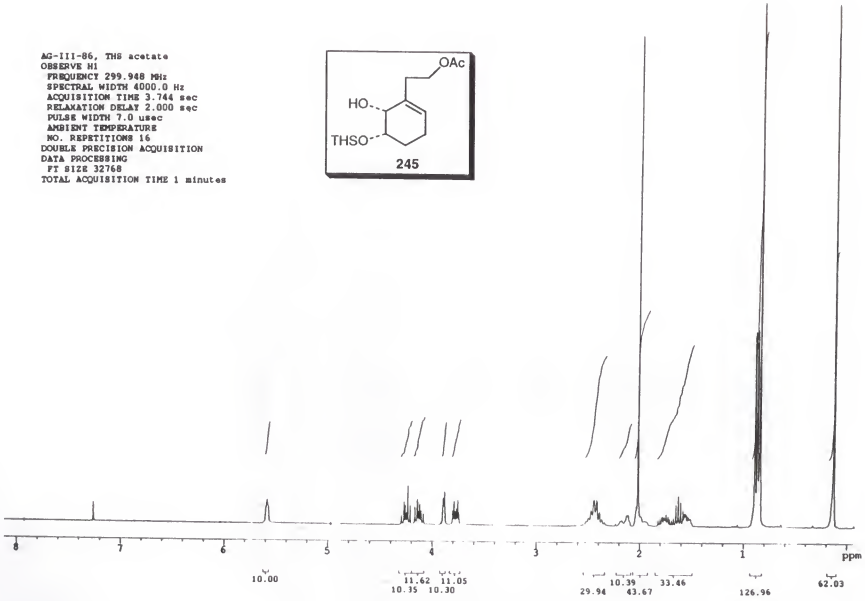

AG-III-85, acetate diol
OBSERVE H1
FREQUENCY 299.948 MHz
SPECTRAL WIDTH 4000.0 Hz
ACQUISITION TIME 3.744 sec
RELAXATION DELAY 2.000 sec
PULSE WIDTH 7.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 16
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
FT SIZE 32768
TOTAL ACQUISITION TIME 1 minutes
OAc
HO
HO
244
9
8
7
6
5
4
3
2
1
0
ppm
10.00
10.06
21.17
10.15
22.78
11.63
21.13
21.10
39.87

AG-III-85, acetate diol
PULSE SEQUENCE apt
OBSERVE C13
FREQUENCY 75.430 MHz
SPECTRAL WIDTH 20000.0 Hz
ACQUISITION TIME 1.814 sec
RELAXATION DELAY 0.000 sec
PULSE WIDTH 8.7 usec
FIRST PULSE WIDTH 26.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 320
DECOUPLE H1
HIGH POWER 64
DECOUPLER GATED ON DURING ACQUISITION
WALTZ16 MODULATED
DATA PROCESSING
LINE BROADENING 1.0 Hz
FT SIZE 131072
TOTAL ACQUISITION TIME 9 minutes

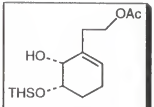


244

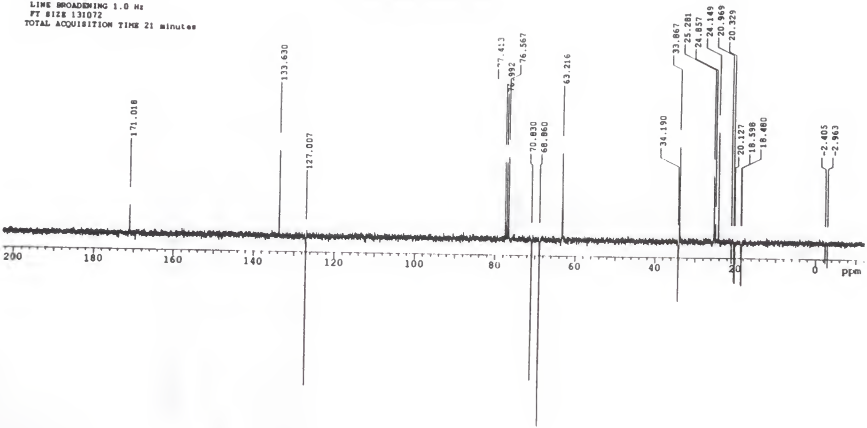


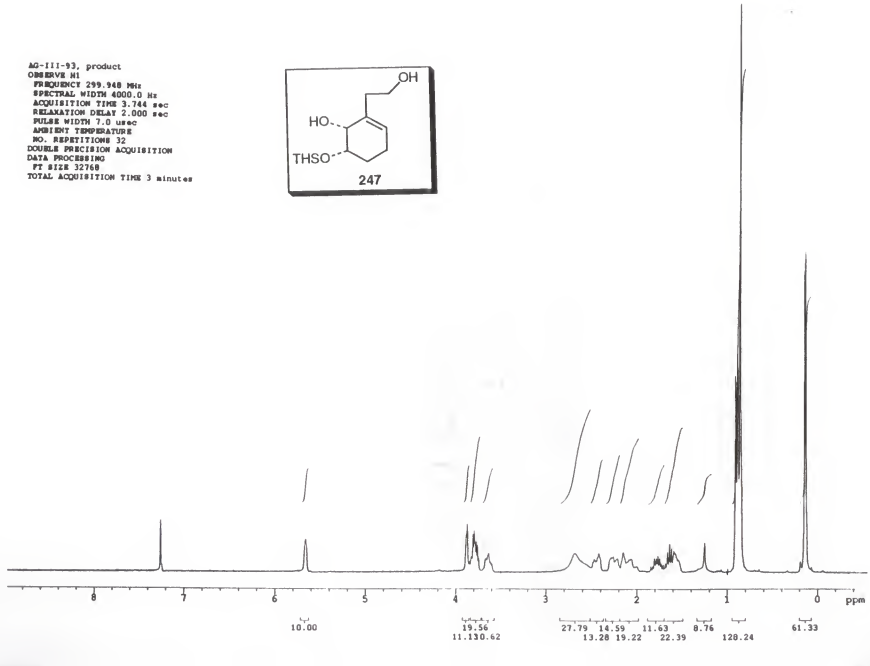

AG-III-86, THS acetate
OBSERVE H1
FREQUENCY 299.948 MHz
SPECTRAL WIDTH 4000.0 Hz
ACQUISITION TIME 3.744 sec
RELAXATION DELAY 2.000 sec
PULSE WIDTH 7.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 16
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
FT SIZE 32768
TOTAL ACQUISITION TIME 1 minutes
OAc
HO
THSO
245
8
7
6
5
4
3
2
1
ppm
10.00
11.62
11.05
10.35
10.30
29.94
10.39
43.67
33.46
126.96
62.03

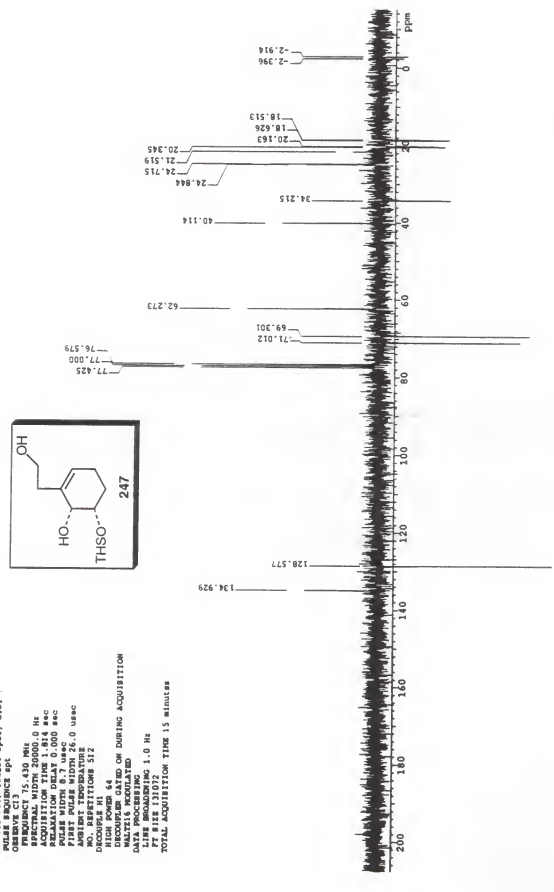
AG-III-86, monoTHS acetate
PULSE SEQUENCE spt
OBSERVE C13
FREQUENCY 75.430 MHz
SPECTRAL WIDTH 20000.0 Hz
ACQUISITION TIME 1.814 sec
RELAXATION DELAY 0.000 sec
PULSE WIDTH 8.7 usec
FIRST PULSE WIDTH 26.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 704
DECOUPLE H1
HIGH POWER 64
DECOUPLER GATED ON DURING ACQUISITION
WALTZ16 MODULATED
DATA PROCESSING
LINE BROADENING 1.0 Hz
FT SIZE 131072
TOTAL ACQUISITION TIME 21 minutes

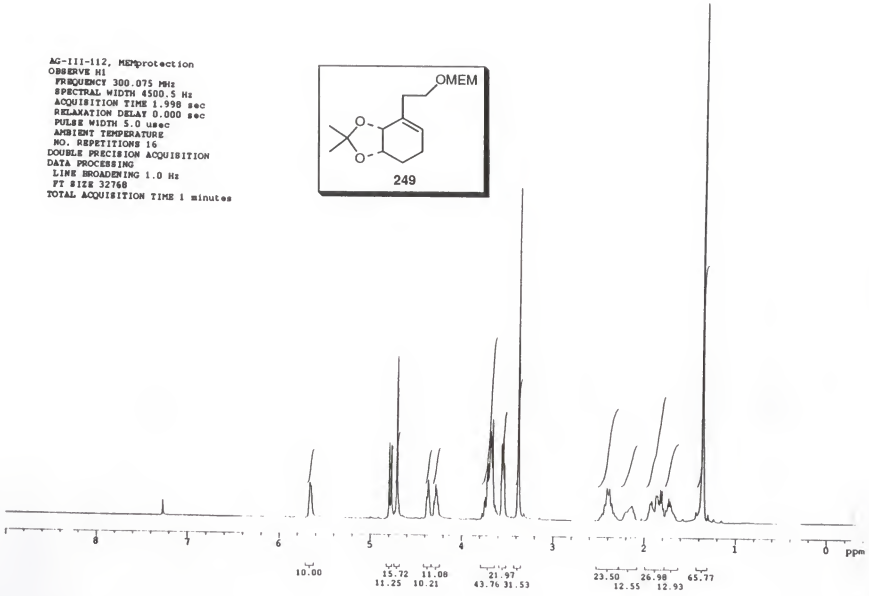


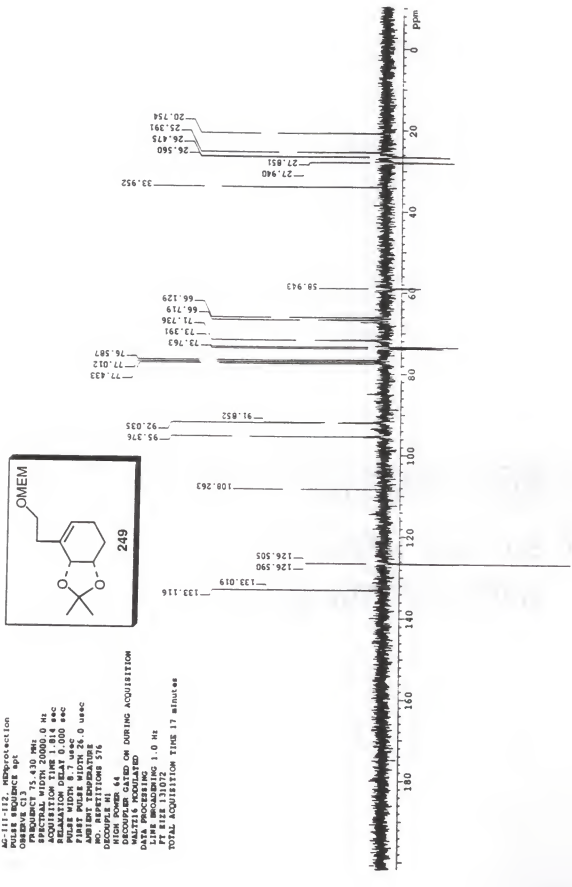
245

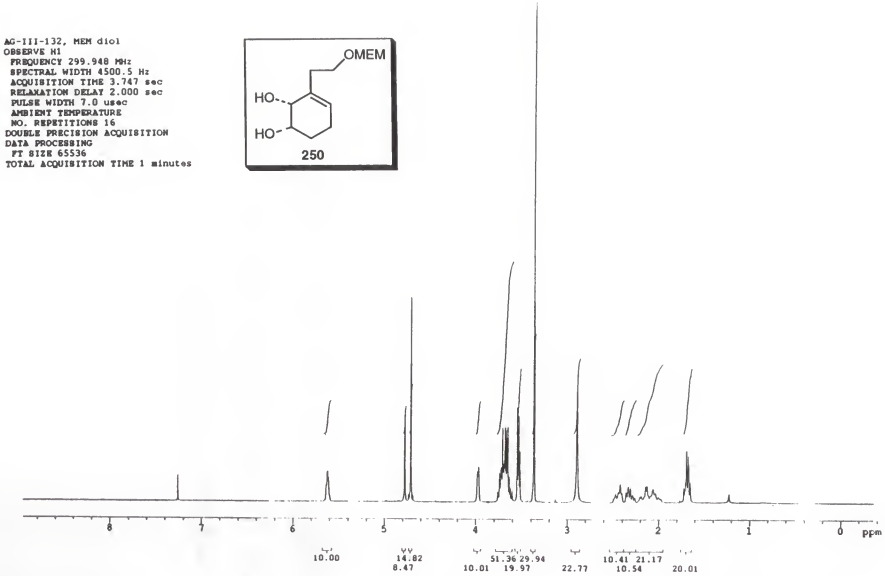


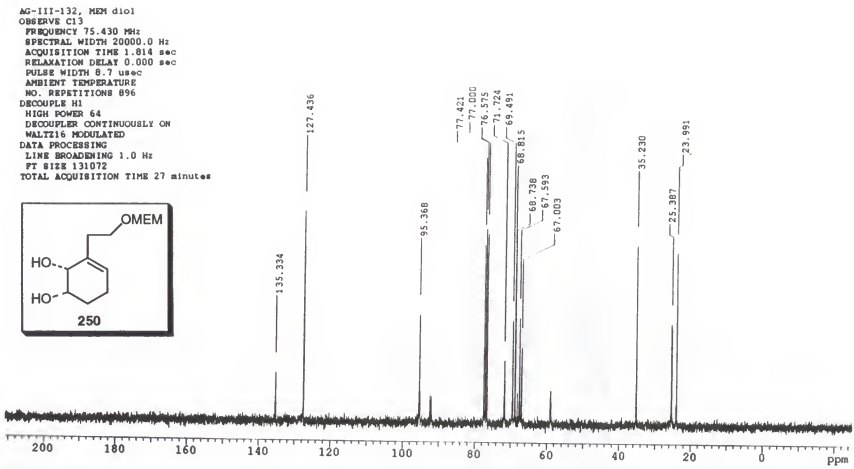

AG-III-93, product
OBSERVE H1
FREQUENCY 299.948 MHz
SPECTRAL WIDTH 4000.0 Hz
ACQUISITION TIME 3.744 sec
RELAXATION DELAY 2.000 sec
PULSE WIDTH 7.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 32
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
FT SIZE 32768
TOTAL ACQUISITION TIME 3 minutes
OH
HO
THSO
247
8
7
6
5
4
3
2
1
0
ppm
10.00
19.56
11.130.62
27.79
14.59
13.28 19.22
11.63
22.39
8.76
120.24
61.33

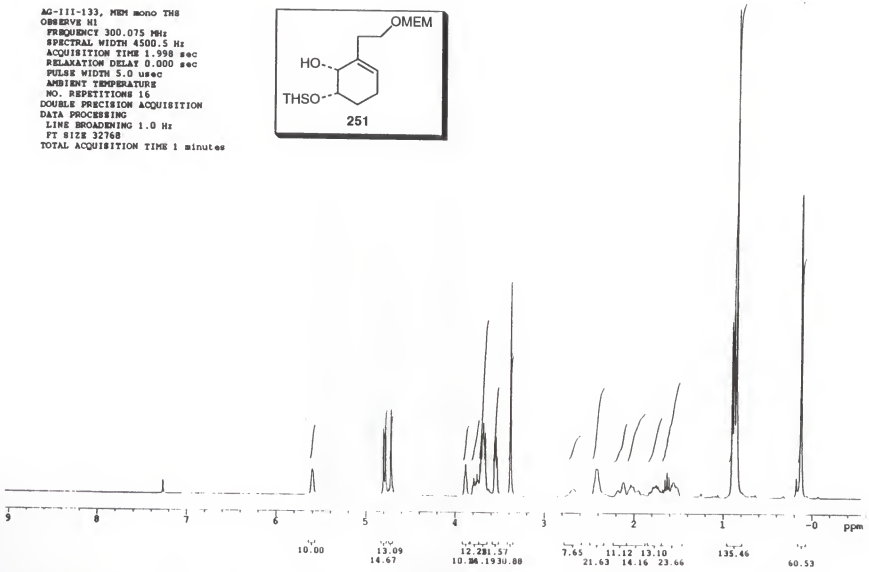

AG-111-103, lowest spot, diol!
PULSE SEQUENCE apt
CHANNEL f1
FREQUENCY 75.430 MHz
SPECTRAL WIDTH 20000.0 Hz
ACQUISITION TIME 1.638 sec
RELAXATION DELAY 1.000 sec
PULSE WIDTH 8.7 usec
FIXED PULSE WIDTH 26.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 512
DECOUPLER f2
HIGH POWER
DECOUPLER GATED ON DURING ACQUISITION
NUCLEUS DECOUPLED
DATA PROCESSING
LINE BROADENING 1.0 Hz
FT of 32768 points
TOTAL ACQUISITION TIME 15 minutes
OH
HO
THSO
247
77.425
77.000
76.579
74.012
69.301
62.273
40.114
34.215
24.844
24.715
21.519
20.345
20.163
18.626
18.513
2.396
2.914
128.577
134.929
ppm


AG-III-112, MEMprotection
OBSERVE H1
FREQUENCY 300.075 MHz
SPECTRAL WIDTH 4500.5 Hz
ACQUISITION TIME 1.998 sec
RELAXATION DELAY 0.000 sec
PULSE WIDTH 5.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 16
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
LINE BROADENING 1.0 Hz
FT SIZE 32768
TOTAL ACQUISITION TIME 1 minutes
OMEM
249
8
7
6
5
4
3
2
1
0
ppm
10.00
15.72
11.25
11.08
10.21
21.97
43.76
31.53
23.50
12.55
26.90
12.93
65.77

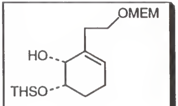

AC-111-f12, MEMprotection
PULSE SEQUENCE sgt
OBSERVE C13
FREQUENCY 75.430 MHz
SPECTRAL WIDTH 20000.0 Hz
ACQUISITION TIME 1.814 sec
RELAXATION DELAY 0.000 sec
PULSE WIDTH 17.500 usec
FIRST PULSE WIDTH 26.0 usec
AMBIENT TEMPERATURE
NO. OF REPETITIONS 516
DECOUPLE HI
HIGH POWER 64
WALTZ16 MODULATED ON DURING ACQUISITION
WALTZ16 MODULATED
DATA PROCESSING
LINE BROADENING 1.0 Hz
FT SIZE 131072
TOTAL ACQUISITION TIME 17 minutes
OMEM
249
133.116
133.019
126.590
126.505
108.263
95.376
92.035
91.852
77.433
77.012
76.587
73.763
73.391
71.736
66.749
66.129
58.943
33.952
27.960
27.851
26.560
26.475
25.391
20.754
ppm


AG-III-132, MEM diol
OBSERVE H1
FREQUENCY 299.948 MHz
SPECTRAL WIDTH 4500.5 Hz
ACQUISITION TIME 3.747 sec
RELAXATION DELAY 2.000 sec
PULSE WIDTH 7.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 16
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
FT SIZE 65536
TOTAL ACQUISITION TIME 1 minutes
OMEM
HO
HO
250
8
7
6
5
4
3
2
1
0
ppm
10.00
14.82
8.47
51.36
29.94
10.01
19.97
22.77
10.41
21.17
10.54
20.01

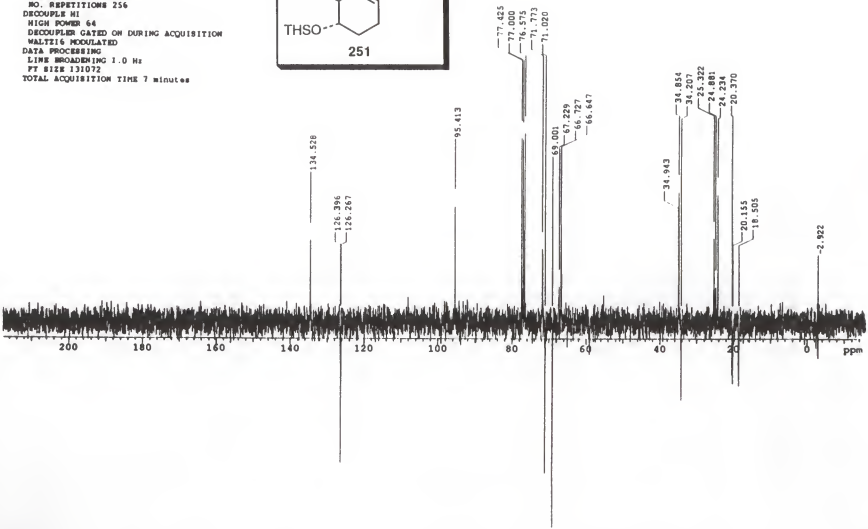

AG-III-132, MEM diol
OBSERVE C13
FREQUENCY 75.430 MHz
SPECTRAL WIDTH 20000.0 Hz
ACQUISITION TIME 1.814 sec
RELAXATION DELAY 0.000 sec
PULSE WIDTH 8.7 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 896
DECOUPLE H1
HIGH POWER 64
DECOUPLER CONTINUOUSLY ON
WALTZ16 MODULATED
DATA PROCESSING
LINE BROADENING 1.0 Hz
FT SIZE 131072
TOTAL ACQUISITION TIME 27 minutes
OMEM
HO
HO
250
135.334
127.436
95.368
77.421
77.000
76.575
74.724
69.491
68.815
68.738
67.593
67.003
35.230
25.387
23.991
200
180
160
140
120
100
80
60
40
20
0
ppm

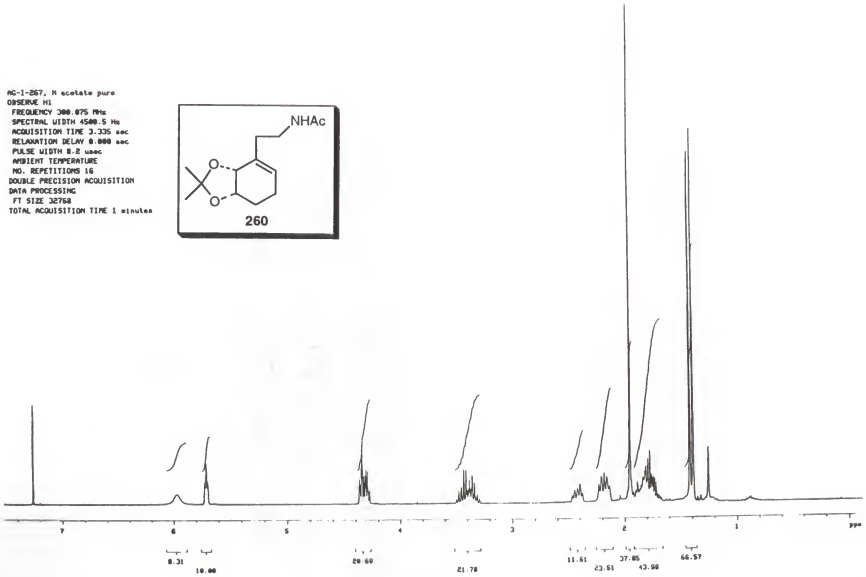

AG-III-133, MEM mono THS
OBSERVE H1
FREQUENCY 300.075 MHz
SPECTRAL WIDTH 4500.5 Hz
ACQUISITION TIME 1.998 sec
RELAXATION DELAY 0.000 sec
PULSE WIDTH 5.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 16
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
LINE BROADENING 1.0 Hz
FT SIZE 32768
TOTAL ACQUISITION TIME 1 minutes
OMEM
HO
THSO
251
ppm
10.00
13.09
14.67
12.28
1.57
10.84
1930.88
7.65
11.12
13.10
21.63
14.16
23.66
135.46
60.53

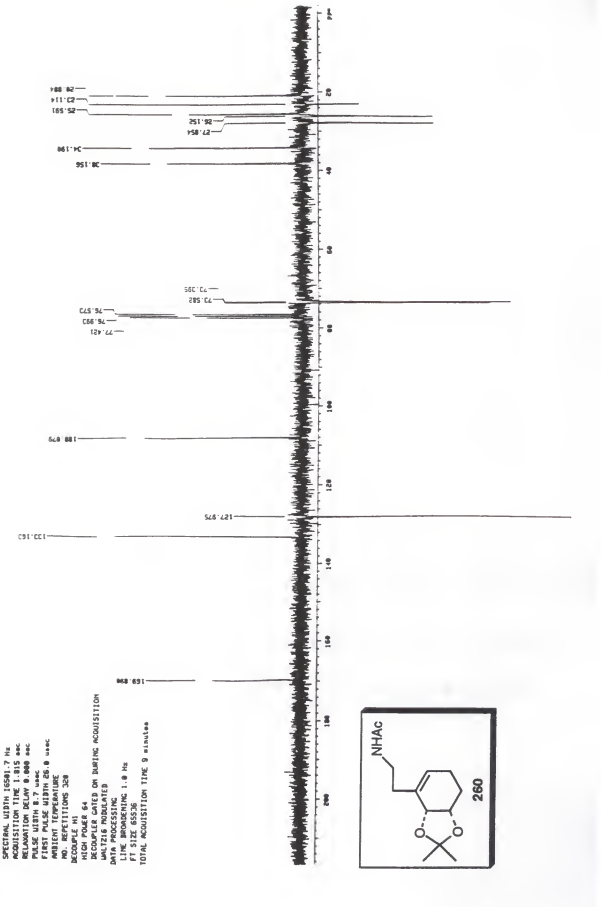
AG-III-133
PULSE SEQUENCE apt
OBSERVE C13
FREQUENCY 75.430 MHz
SPECTRAL WIDTH 20000.0 Hz
ACQUISITION TIME 1.814 sec
RELAXATION DELAY 0.000 sec
PULSE WIDTH 8.7 usec
FIRST PULSE WIDTH 26.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 256
DECOUPLE HI
HIGH POWER 64
DECOUPLER GATED ON DURING ACQUISITION
WALTZ16 MODULATED
DATA PROCESSING
LINE BROADENING 1.0 Hz
FT SIZE 131072
TOTAL ACQUISITION TIME 7 minutes



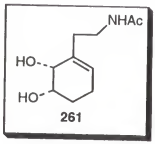
251



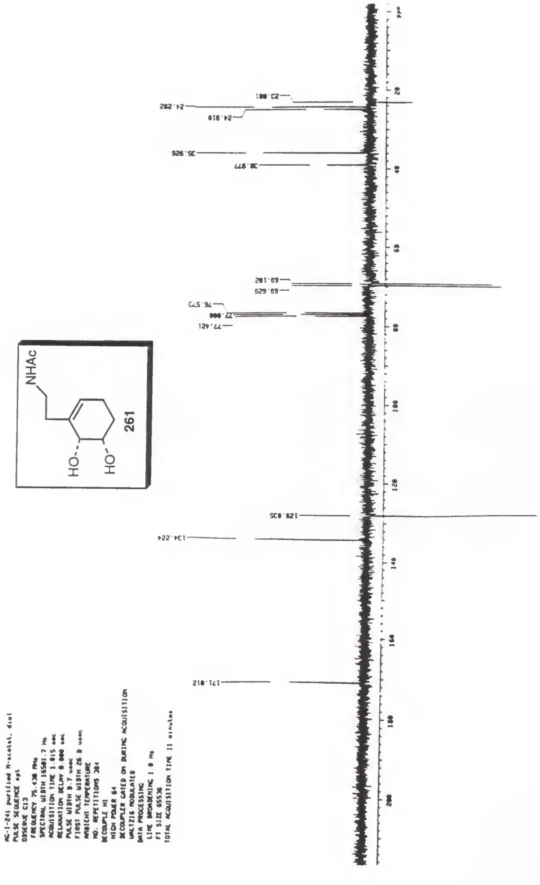

AC-1-267, H acetate pure
OBSERVE H1
FREQUENCY 300.075 MHz
SPECTRAL WIDTH 4500.5 Hz
ACQUISITION TIME 3.335 sec
RELAXATION DELAY 0.000 sec
PULSE WIDTH 8.2 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 16
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
FT SIZE 32768
TOTAL ACQUISITION TIME 1 minutes
NHAc
260
7
6
5
4
3
2
1
ppm
8.31
10.00
20.69
21.78
11.61
23.51
37.85
43.98
66.57

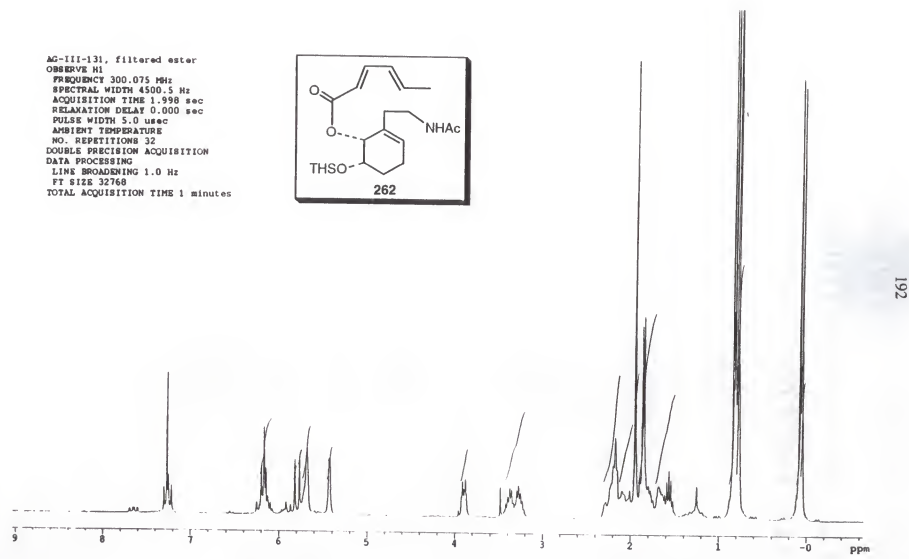

AC-1-230 Pyridine
PULSE SEQUENCE: ap1
OBSERVE C13
FREQUENCY 75. 4 MHz
SPECTRAL WIDTH 15041.7 Hz
ACQUISITION TIME 1.815 sec
RELAXATION DELAY 0.000 sec
PULSE WIDTH 7.5 usec
FIRST PULSE WIDTH 23.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 320
DECOUPLE HI
HIGH POWER 64
WALTZ16 MODULATED
DATA PROCESSING
LINE BROADENING 1.0 Hz
FT SIZE 65536
TOTAL ACQUISITION TIME 9 minutes
NHAc
260

AG-III-72, acetamide diol
OBSERVE H1
FREQUENCY 300.075 MHz
SPECTRAL WIDTH 4500.5 Hz
ACQUISITION TIME 1.998 sec
RELAXATION DELAY 2.000 sec
PULSE WIDTH 5.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 16
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
LINE BROADENING 1.0 Hz
FT SIZE 32768
TOTAL ACQUISITION TIME 1 minutes



261


AC-1-241 purified N-acetyl, diol
PULSE SEQUENCE apt
OBSERVE C13
FREQUENCY 75.430 MHz
SPECTRAL WIDTH 16501.7 Hz
ACQUISITION TIME 1.815 sec
RELAXATION DELAY 0.000 sec
PULSE WIDTH 8.7 usec
FIRST PULSE WIDTH 26.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 384
DECOUPLE H1
HIGH POWER 64
DECOUPLER GATED ON DURING ACQUISITION
WALTZ16 MODULATED
DATA PROCESSING
LINE BROADENING 1.0 Hz
FT SIZE 65536
TOTAL ACQUISITION TIME 11 minutes
NHAc
HO
HO
261
171.012
134.224
128.035
77.421
77.000
76.573
69.629
69.102
38.977
35.926
24.918
24.282
23.081
200
180
160
140
120
100
80
60
40
20
ppm


AG-III-131, filtered ester
OBSERVE H1
FREQUENCY 300.075 MHz
SPECTRAL WIDTH 4500.5 Hz
ACQUISITION TIME 1.998 sec
RELAXATION DELAY 0.000 sec
PULSE WIDTH 5.0 usec
AMBIENT TEMPERATURE
NO. REPETITIONS 32
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
LINE BROADENING 1.0 Hz
FT SIZE 32768
TOTAL ACQUISITION TIME 1 minutes
O
O
NHAc
THSO
262
9
8
7
6
5
4
3
2
1
-0
ppm
18.27
16.12
9.03
10.00
10.00
21.50
32.66
33.56
27.20
18.25
0.74
65.66
67.54
31.23
29.92

AC-III-131, filtered ester
PULSE SEQUENCE zgtc
OBSERVE C13
FREQUENCY 75.462 MHz
SPECTRAL WIDTH 18761.7 Hz
ACQUISITION TIME 0.873 sec
RELAXATION DELAY 0.000 sec
PULSE WIDTH 5.0 usec
POWER LEVEL (TOTAL) 31.8 usec
AMBIENT TEMPERATURE
NO. REPETITIONS# 4096
DECOUPLE H1
POWER LEVEL 10
DECOUPLER GATED ON DURING ACQUISITION
WALTZ16 MODULATED
DOUBLE PRECISION ACQUISITION
DATA PROCESSING
LINE BROADENING 3.5 Hz
FT SIZE 32768
TOTAL ACQUISITION TIME 55 minutes
NHAc
THSO
262
165.427
139.463
132.284
129.871
129.006
119.081
77.485
76.635
70.822
68.971
36.377
34.218
33.809
26.600
24.870
24.096
23.353
20.242
18.587
-2.780
ppm

LIST OF REFERENCES

1. F. Santavy, Alkaloids, New York, **17**, (1979), 385.

2. C.E. Terry and M. Pellens, The Opium Problem, Ch. 2, *Bur. Soc. Hyg.*, New York, 1928.

3. J.F. Deronse, *Ann. Chim.*, **45**, (1803), 257.

4. M.A. Seguin, *Ann. Chim.*, **92**, (1806), 225.

5. F.W.A. Sertürner, *Trommdorff's J. Pharm.*, **14**, (1806), 47.

6. J.M. Gulland and R. Robinson, *Proc. Mem. Manchester Lit. Phil. Soc.*, **69**, (1925), 79.

7. i. M. Gates and G. Tschudi, *J. Am. Chem. Soc.*, **74**, (1952), 1109.
   ii. M. Gates and G. Tschudi, *J. Am. Chem. Soc.,* **78**, (1954), 1380.

8. M.A. Tius and M.A. Kerr, *J. Am. Chem. Soc.*, **114**, (1992), 5959.

9. D. Elad and D. Ginsburg, *J. Am. Chem. Soc.*, **76**, (1954), 312.

10. D.H.R. Barton, G.W. Kirby, W. Steglich, and G.M. Thomas, *Proc. Chem. Soc.*, (1963), 203.

11. i. R. Grewe and W. Friedrichsen, *Chem. Ber.*, **100**, (1967), 1550.
    ii. R. Grewe, H. Fischer, and W. Friedrichsen, *Chem. Ber.*, **100**, (1967), 1.
    iii. R. Grewe and H. Fischer, *Chem. Ber.*, **96**, (1963), 1520.

12. G.C. Morrison, R.P. Waite, and J. Shavel, Jr., *Tetrahedron Lett.*, (1967), 4055.

13. T. Kametani, M. Ihara, K. Fukumoto, and H. Yagi, *J. Chem. Soc., Chem. Commun.,* (1969), 2030.

14. i. M.A. Schwartz and I.S. Mami, *J. Am. Chem. Soc.*, **97**, (1975), 1239.
    ii. M.A. Schwartz and P.T.K. Pham, *J. Org. Chem.*, **53**, (1988), 2318.

15. T.S. Lie, L. Maat, and H.C. Beyerman, *Recl. Trav. Chim. Pays-Bas*, **98**, (1979), 419.

16. K.C. Rice, *J. Org. Chem.*, **45**, (1980), 3135.

17. D.A. Evans, and C.H. Mitch, *Tetrahedron Lett.*, **23**, (1982), 285.

18. W.H. Moos, R.D. Gless, and H.J. Rapoport, *J. Org. Chem.*, **48**, (1983), 227.

19. J.D. White, G. Caravatti, T.B. Kline, E. Edstrom, K.C. Rice, and A. Brossi, *Tetrahedron*, **39**, (1983), 2393.

20. W. Ludwig and H.J. Schäfer, *Angew. Chem., Int. Ed. Engl.*, **25**, (1986), 1025.

21. J.E. Toth and P.L. Fuchs, *J. Org. Chem.*, **52**, (1987), 473.

22. R.B. Barber and H. Rapoport, *J. Med. Chem.*, **19**, (1976), 1175.

23. K.A. Parker and D. Fokas, *J. Am. Chem. Soc.*, **114**, (1992), 9688.

24. C.Y. Hong, N. Kado, and L.E. Overman, *J. Am. Chem. Soc.*, **115**, (1993), 11028.

25. J. Mulzer, G. Dümer, and D. Trauner, *Angew. Chem., Int. Ed. Engl.*, **35**, (1996), 2830.

26. O. Diels and K. Alder, *Justus Liebigs Ann. Chem.,* **460**, (1928), 98.

27. i. J.A. Norton, *Chem. Rev.,* **31**, (1942), 319.
ii. M.C. Kloetael, *Org. React.,* **4**, (1948), 1.
iii. L.W. Butz and A.W. Rytina, *Org. React.*, **5**, (1949), 136.
iv. A. Wasserman, Diels-Alder Reactions, Elsevier, New York, 1965.
v. W. Oppolzer, "Intermolecular Diels-Alder Reaction" in Comprehensive Organic Synthesis, B.M. Trost, ed., Pergamon Press, New York, Vol. 5, (1991), 315.

28. R.B. Woodward and R. Hoffmann, The Conservation of Orbital Symmetry, Verlag Chemie, Weinheim, Germany, (1970).

29. I. Flemming, Frontier Orbitals and Organic Chemical Reactions, John Wiley & Sons, New York, (1976).

30. K. Alder and M. Schumaker, *Fortschr. Chem. Org. Naturst.*, **10**, (1953), 66.

31. i. G. Brieger, *J. Am. Chem. Soc.,* **87**, (1963), 3783.
ii. L.H. Klemm and K.W. Gopinath, *Tetrahedron Lett.*, **4**, (1963), 1243.

32. i. W. Oppolzer, *Angew. Chem., Int. Ed. Engl.,* **16**, (1977), 10.
ii. W. Oppolzer, *Synthesis*, (1978), 798.
iii. R.L. Funk and K.P.C. Vollhardt, *Chem. Soc. Rev.*, **9**, (1980), 41.
iv. G. Brieger and J.N. Bennett, *Chem. Rev.,* **80**, (1980), 63.
v. D.F. Taber, "Intramolecular Diels-Alder Reactions and Alder Ene Reactions", Springer Verlag, New York, (1984).
vi. E. Ciganek, *Org. React.*, **32**, (1984), 1.
vii. A.G. Fallis, *Can. J. Chem.,* **62**, (1984), 183.
viii. D. Craig, *Chem. Soc. Rev.*, **16**, (1987), 187.
ix. W.R. Roush, "Intramolecular Diels-Alder Reaction" in Comprehensive Organic Synthesis, B.M. Trost, ed., Pergamon Press, New York, Vol. 5, (1991), 513.

33. K.J. Shea, S. Wise, L.D. Burke, P.D. Davis, J.W. Gilman, and A.C. Greenley, *J. Am. Chem. Soc.*, **104**, (1982), 5708.

34. H.O. House and T.H. Cronin, *J. Org. Chem.*, **30**, (1965), 1061.

35. i. R.K. Boeckman, Jr. and S.S. Ko, *J. Am. Chem. Soc.*, **102**, (1980), 7146.
ii. R.K. Boeckman, Jr. and S.S. Ko, *J. Am. Chem. Soc.*, **104**, (1982), 1033.

36. W.R. Roush, *J. Org. Chem.*, **44**, (1979), 4008.

37. W.R. Roush, H.R. Gillis, and A.I. Ko, *J. Am. Chem. Soc.*, **104**, (1982), 2269.

38. Y. Lin and K.N. Houk, *Tetrahedron Lett.*, **26**, (1985), 2269.

39. J.J.S. Bajorek and J.K. Sutherland, *J. Chem. Soc., Perkin Trans. 1*, (1975), 1559.

40. M.E. Jung and K.M. Halweg, *Tetrahedron Lett.*, **22**, (1981), 3929.

41. T. Wu and K.N. Houk, *Tetrahedron Lett.*, **26**, (1985), 2293.

42. F.K. Brown and K.N. Houk, *Tetrahedron Lett.*, **26**, (1985), 2297.

43. M. Ihara, A. Kawaguchi, H. Ueda, M. Chihiro, K. Fukumoto, and T. Kametani, *J. Chem. Soc., Perkin Trans. 1*, (1987), 1331.

44. M.G. Brasca, H.B. Broughton, D. Craig, S.V. Ley, A.A. Somovilla, and P.L. Toogood, *Tetrahedron Lett.*, **29**, (1988), 1853.

45. M.J. Kurth, M.J. O'Brien, H. Hope, and M. Yanuck, *J. Org. Chem.*, **50**, (1985), 2626.

46. R.S. Mkrtchyan, T.R. Melikyan, G.O. Torosyan, K.T. Tagmazyan, and A.T. Babayan, *Arm. Khim. Zh.*, **30**, (1978), 328. [*C.A.*, **89**, 108932 (1978)]

47. W.R. Roush, *J. Am. Chem. Soc.*, **100**, (1978), 3599.

48. W. Oppolzer and R.L. Snowden, *Tetrahedron Lett.*, **46**, (1976), 4187.

49. R.F. Borch, A.J. Evans, and J.J. Wade, *J. Am. Chem. Soc.*, **97**, (1975), 6282.

50. G.A. Kraus and M.J. Taschner, *J. Am. Chem. Soc.*, **102**, (1980), 1974.

51. P. Yates and P E. Eaton, *J. Am. Chem. Soc.*, **82**, (1960), 4436.

52. K.N. Houk, *Acc. Chem. Res.*, **8**, (1975), 361.

53. P.G. Gassman and D.A. Singleton, *J. Am. Chem. Soc.*, **106**, (1984), 6085.

54. W.R. Roush, H.R. Gillis, and A.P. Essenfeld, *J. Org. Chem.*, **49**, (1984), 4647.

55. P.A. Wender and T.E. Jenkins, *J. Am. Chem. Soc.,* **111**, (1989), 6432.

56. R.S. Jolly, G. Luedtke, D. Sheehan, and T. Livinghouse, *J. Am. Chem. Soc.,* **112**, (1990), 4965.

57. A. Lubineau, J. Auge, and Y. Queneau, *Synthesis*, (1994), 741.

58. D.C. Rideout and R. Breslow, *J. Am. Chem. Soc.,* **102**, (1980), 7816.

59. L.A. Van Royen, R. Mijingheer, and P.J. De Clercq, *Tetrahedron Lett.*, **26**, (1985), 4667.

60. i. K. Matsumoto, A. Sera, and T. Uchida, *Synthesis*, (1985), 1.
ii. K. Matsumoto and A. Sera, *Synthesis*, (1985), 999.
iii. R.J. Giguere, in OrganicSynthesis: Theory and Applications, JAI Press, Inc., Greenwich, CT, (1989), 103.

61. W.G. Dauben and H.O. Krabbenhoft, *J. Am. Chem. Soc.,* **98**, (1976), 1992.

62. i. S.J. Burrell, A.E. Derome, M.S. Edenborough, L.M. Harwood, S.A. Leeming, and N.S. Isaacs, *Tetrahedron Lett.*, **26**, (1985), 2229.
ii. N.S. Isaacs and P. Van der Beeke, *Tetrahedron Lett.*, **23**, (1982), 2147.

63. B.A. Keay and P.W. Dibble, *Tetrahedron Lett.*, **30**, (1989), 1045.

64. P.J. DeClercq and L.A. Van Royen, *Synthetic Commun.*, **9**, (1979), 771.

65. D.D. Sternbach and D.M. Rossana, *J. Am. Chem. Soc.,* **104**, (1982), 5853.

66. i. B.A. Keay, *J. Chem. Soc., Chem. Commun.*, (1987), 419.
ii. D.D. Sternbach and D.M. Rossana, *Tetrahedron Lett.*, **23**, (1982), 303.

67. i. R. Gedye, F. Smith, K. Westaway, A. Humera, L. Baldisera, L. Laberge, and J. Rousell, *Tetrahedron Lett.*, **27**, (1986), 279.
ii. R.J. Giguere, T.L. Bray, S.M. Duncan, and G. Majetich, *Tetrahedron Lett.*, **27**, (1986), 4945.

68. W.E. Backmann and L.B. Scott, *J. Am. Chem. Soc.,* **70**, (1948), 1458.

69. i. K.S. Suslick, D.A. Hammerton, and R.E. Cline, Jr., *J. Am. Chem. Soc.,* **109**, (1986), 5641.
ii. K.S. Suslick, D.A. Hammerton, and R.E. Cline, Jr.,*Ultrason. Symp. Proc.*, **2**, (1985), 1116.

70. J. Lee and J.K. Snyder, *J. Am. Chem. Soc.,* **111**, (1989), 1522.

71. T.P. Caulier and J. Reisse, *J. Org. Chem.,* **61**, (1996), 2547.

72. A.J. Bartlett, T. Laird, and W.D. Ollis, *J. Chem. Soc., Chem. Commun.*, (1974), 496.

73. S.D. Burke, S.M. Smith Strickland, and T.H. Powner, *J. Org. Chem.*, **48**, (1983), 454.

74. R.L. Funk, C.J. Mossman, and W.E. Zeller, *Tetrahedron Lett.*, **25**, (1984), 1655.

75. K. Hayakawa, S. Ohsuki, and K. Kanematsu, *Tetrahedron Lett.*, **27**, (1986), 947.

76. L.H. Klemm, K.W. Gopinath, D. Hsu Lee, F.W. Kelly, E. Trod, and T.M. McGuire, *Tetrahedron*, **22**, (1966), 1797.

77. R.K. Boeckman, Jr. and D.M. Demko, *J. Org. Chem.*, **47**, (1982), 1789.

78. i. W. Oppolzer and W. Frostl, *Helv. Chim. Acta*, **58**, (1975), 590.
ii. W. Oppolzer and K. Keller, *J. Am. Chem. Soc.*, **93**, (1971), 3836.

79. F.E. Ziegler, B.H. Jaynes, and M.T. Saindane, *Tetrahedron Lett.*, **26**, (1985), 3307.

80. E. Ciganek, *J. Am. Chem. Soc.,* **103**, (1981), 6261.

81. S. Handa, K. Jones, C.G. Newton, and D.J. Williams, *J. Chem. Soc., Chem. Commun.*, (1985), 1362.

82. T. Kametani, Y. Suzuki, and T. Honda, *J. Chem. Soc., Perkin Trans. 1,* (1986), 1373.

83. M.J. Constanzo, *Ph.D. Thesis presented to Temple Univ.*, Philadelphia, (1988).

84. C. Wu, *Ph.D. Thesis presented to Columbia Univ.*, New York, (1990).

85. T. Hudlicky, C.H. Boros, and E.E. Boros, *Synthesis*, (1992), 174.

86. M.R. Stabile, T. Hudlicky, M.L. Meisels, *Tetrahedron: Assym.* **6**(2), (1995), 537.

87. A.M. Jeffrey, H.J.C. Yeh, D.M. Jerina, T.R. Patel, J.F. Davey, and D.T. Gibson, *Biochemistry*, **14**, (1975), 575.

88. M.R. Stabile, T. Hudlicky, M.L. Meisels, G. Butora, A.G. Gum, S.P. Fearnley, A.J. Thorpe, and M.R. Ellis, *Chirality*, **7**, (1995), 556.

89. K. Mori, *Tetrahedron*, **30**, (1974), 3807.

90. T. Hudlicky, M.A.A. Endoma, and G. Butora, *J. Chem. Soc. Perkin Trans. 1*, (1996), 2187.

91. G. Butora, A.G. Gum, T. Hudlicky, and K.A. Abboud, *Synthesis* (submitted May 1997)

92. M. Kinoshita, H. Takami, M. Taniguchi, and T. Tamai, *Bull. Chem. Soc. Jpn.,* (1987), **60**, 2151.

93. L. Crombie, M.A. Horsham, and S.R.M. Jarrett, *J. Chem Soc., Perkin Trans. I*, (1991), 1511.

94. M. Mladenova, M. Alami, and G. Linstrummelle, *Tetrahedron Lt.*, **37**(36), (1996), 6547.

95. M. Alami, S. Gueugnot, E. Domingues, and G. Linstrummelle, *Tetrahedron*, **51**, (1995), 1209.

96. P.J. Jessip, C.B. Petty, J. Roos, and L.E. Overman, *Org. Syn.*, **59**, (1980), 1.

97. H.E. Ungnade and T.R. Hopkins, *J. Am. Chem. Soc.*, **73**, (1951), 3091.

98. B.L. Pagenkopf, D. O'Mahony, and T. Livinghouse, "Stereocontrolled Carboannulation via Transition Metal Complexes," paper presented at the *7th Symposium on the Latest Trends in Organic Synthesis*, October 23-27, 1996, Gainesville, FL.

99. H. Nakanishi, and M. Oki, *Bull. Chem. Soc. Jpn.*, **43**, (1970), 2558.
ii. H. Wennerstrom, S. Forsen, and B. Roos, *J. Phys. Chem.*, **76**, (1972), 2436.
iii. H. Nakanishi, H. Fujita, and O. Yamamoto, *Bull. Chem. Soc. Jpn.*, **51**, (1978), 214.
iv. J.K. Wilmshurst, *J. Mol. Spectrosc.*, **1**, (1957), 201.

BIOGRAPHICAL SKETCH

Andrew G. Gum was born in Midland, Michigan, on September 6, 1968. He was the third son in a family of four children (Will, Charlie, and younger sister Tammi) born to parents Dr. Wilson F. Gum, Jr. and Barbara J. Gum. As a child he always had an interest in camping, music, and sports and enjoyed these activities with family and friends.

After moving to Texas at the age of 6, he became active both in the Boy Scouts of America as a Cub Scout and with local soccer and little league baseball organizations. Interest in the Boy Scouts has continued through much of his life, culminating with his receiving the Eagle Scout Award in 1983. He also had the fortune of attending both National (Fort A.P. Hill, Virginia, 1981) and World Scout Jamborees (Alberta, Canada, 1983), providing him with the opportunity to meet young people from many different states and nations. He also spent two summers at Camp Rotary, (Clare, Michigan, 1982-83) as a staff member and also at the National Scout Jamboree (Fort A.P. Hill, Virginia, 1985) as a member of the dining hall youth staff, which gave him his first experiences in leading and teaching. He also had the opportunity to visit two of the Boy Scouts of America's largest high adventure parks (Philmont, New Mexico, and Florida Sea Base, The Keys, Florida), where he experienced hiking and living in the Rocky Mountains and the basics of operating a 7 crew-member sail boat.

Andrew began playing the piano at age 5 and singing with the church choir at the age of 11. Musical interests continued as he participated in several church and community musicals, and he began playing the clarinet in the fourth grade, an activity that continued through high school, where he participated in the concert and marching bands. Interest in athletics also continued as he participated on a variety of local soccer, basketball, and

baseball teams. At age 14, he discovered football and the pole vault, activities he would continue and receive varsity letters for in high school.

Academically, Andrew always had an interest in science and mathematics. He was exposed to the chemical industry by his father, who often took him on visits to Dow Chemical as a youth. These early experiences combined with an encouraging high school chemistry teacher (Mr. Kurth) moved him toward pursuing a career in chemistry.

Andrew was also interested in the possibility of combining a career in chemistry with a career as a military officer, and he applied to the United States Naval Academy while in his senior year at Brazoswood High School (Clute, Texas). He graduated *cum laude* from high school (May, 1987) and received a congressional appointment to the Naval Academy from Rep. Tom Delay (Sugarland, Texas). Although not accepted to the U.S.N.A. directly, he did receive a U.S. Naval Academy Foundation Scholarship, sponsoring him to attend the Northwestern Preparatory School (Santa Barbara, California). After spending one semester at Northwestern P.S., Andrew returned to Texas, choosing to pursue a career in chemistry at Trinity University over accepting an appointment to the U.S.N.A.

Andrew moved to San Antonio, Texas in August of 1988 as a transfer student and enrolled at Trinity University as a chemistry major. While at Trinity, he pursued independent chemical research under the direction of Dr. Nancy S. Mills, who exposed him to organic synthesis and motivated him to continue research in a graduate program. He received a National Science Foundation Fellowship (S.U.R.E.--Summer Undergraduate Research Experience) to pursue independent research (May, 1990). Additionally, Andrew had the opportunity to spend two summers (1989 and 1991) as an intern with the Dow Chemical Co. (Freeport, Texas) where he received first-hand experience with the daily operations of a chemical pilot plant facility. While at Trinity, Andrew continued to pursue other academic interests, including the German language and speech communications. Additionally, he was president of the Trinity University Lacrosse Club (1989-90) where he

participated on the field in competitions with schools across the Southwestern Conference and off the field by obtaining official University Club recognition for the organization. Andrew also was part on an improvisation comedy team (The Crystal Lemmings) and enjoyed performing on the stage on the Trinity campus and at other colleges and night clubs. He graduated with a B.S. in Chemistry from Trinity University in December of 1991.

With the opportunity to study in Switzerland, Andrew flew to Zürich in March of 1992 where he spent 6 months with the Riese Family, longtime family friends. He enrolled for a semester at the University of Zürich, where he was able to visit a variety of university courses and strengthen his German language skills. He also attended the Benedict Language School from which he received a German Diploma (July, 1992).

After returning to the U.S., Andrew prepared to enter graduate school at Virginia Polytechnic and State University (Blacksburg, Virginia). With a continued interest in organic synthesis, Andrew joined the research group of Dr. Tomas Hudlicky at Virginia Tech in the fall of 1992. As a member of the research group, he was exposed to traditional organic synthetic techniques as well as to the fundamentals of microbiology and fermentation technology. The mountainous landscape of Virginia got Andrew interested in the sport of mountain biking, and he also learned how to rollerblade, spending three seasons playing in the Blacksburg RollerHockey League. In the winter of 1995, he followed his research director to the University of Florida, where he continued pursuing an approach to the synthesis of morphine. The highlight of his stay at the University of Florida came in April of 1997 when he presented a research paper at the 213th National American Chemical Society Meeting in San Francisco, California.

Andrew plans to pursue a postdoctoral research position with Dr. Herbert Waldmann at the University of Karlsruhe following the completion of his Ph.D. work. In Germany, he hopes to expand his knowledge and proficiency in both the German language

and in organic synthesis. Ultimately, he wishes to pursue a career as an organic chemist in the pharmaceutical industry.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Tomas Hudlicky, Chairman
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Kenneth B. Wagener
Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Jonathan E. Enholm
Associate Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

James M. Boncella
Associate Professor of Chemistry

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Kenneth B. Sloan
Professor of Medicinal Chemistry

This dissertation was submitted to the Graduate Faculty of the Department of Chemistry in the College of Liberal Arts and Sciences, and to the Graduate School and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

August, 1997

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Dean, Graduate School